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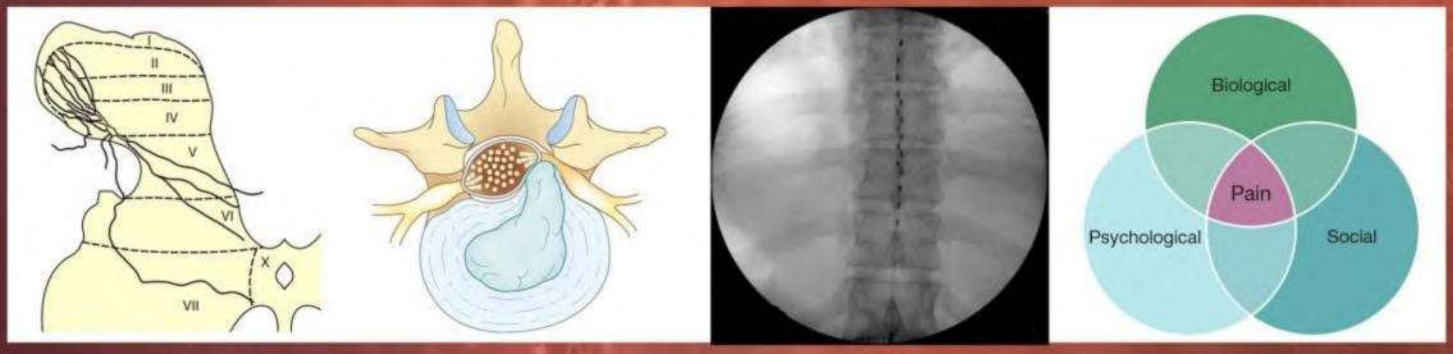

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Practical Management of Pain

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SIXTH EDITION

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ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

PRACTICAL MANAGEMENT OF PAIN, SIXTH EDITION ISBN: 978-0-323-71101-2

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Executive Content Strategist: Michael Houston
Senior Content Development Specialist: Lisa Barnes
Publishing Services Manager: Shereen Jameel
Senior Project Manager: Manikandan Chandrasekaran
Design Direction: Margaret Reid

Printed in India

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To my wife, Juliet – thank you for your encouragement and support.
To our children and their spouses – Hazel and Paul, Hubert and Natalie.
To our grandchildren – Annalisa and Jonathan, Hunter and Jackson.
To my co-editors for working with me over three editions.
To all authors who took time off their busy schedules to write their chapters.
To all patients with pain – with basic, translational, and clinical advances, we hope your suffering will be better understood and treated.

Honorio T. Benzon

To Nori Benzon, who, through yet another revision of this text, this one during the course of a pandemic, led the project with patience, persistence, and kindness; it is a great privilege to work with you.
To my wife and children – Bobbi, Lauren, James, and Cara – thank you for your tremendous support.

James P. Rathmell

This work is dedicated to my parents (Shy-Hsien and Tsai-Lien), children (Emily and Alex), partner (Cynthia Cummis), and mentors. I am grateful for their continued support and encouragement.

Christopher L. Wu

To my many mentors, collaborators, and colleagues; way too many to list, but all of whom have contributed greatly to my understanding of the people and especially the plight of people who experience persistent pain. They have truly enriched my journey. And with gratitude to LORRAINE, more than a wife, a partner, and my best friend; for her consistent and unyielding patience, tolerance, and sacrifices throughout our marriage.

Dennis C. Turk

To my wife and best friend Pat – what an adventure we are having together!
To our children David, Melanie, and Emily – it has been a joy to watch you grow into unique and amazing adults.
To Nori Benzon – for asking me to be a part of this project and for his persistence and diligence in assuring its completion in such a dignified manner. To each of the co-editors – I am so grateful to have had the opportunity to work with and learn from you as we completed this venture together.
And to those who experience acute and chronic pain – it is my sincere hope that our ongoing determination to better understand the multiple mechanisms of pain and how to best treat painful conditions will lead to greater pain relief and less suffering.

Charles E. Argoff

To my wife and best friend, Meredith, for her unending support.
To my daughter, Alexandra, and sons, Sebastian and Gibson, my greatest joys.
To my parents, Morrison and Brenda, and my sister, Erin, who have always kept me grounded.
To my mentors, Donna Hammond, Steve Cohen, and Chris Wu, for fostering my interests and, when needed, reining me in.
To my collaborators, for questioning every sentence I put down on paper.

Robert W. Hurley

To my wife and best friend, Carrie, for showing me the power of authenticity and how embodying that principle allows one to fulfill their greatest potential in life and work. You are my why.
To my children, Stellan and Emmett, your support of mommy's "doctor work" is infinitely appreciated. Keep reaching for the stars; there is no limit to what you can achieve if you are true to yourself.
To Nori Benzon, Rob Hurley, Dan Clauw, Nirmala Abraham, Chad Brummett, and Talal Khan, my mentors, sponsors, and cheerleaders. I have nothing but deep gratitude for the support, guidance, and friendship you have bestowed upon me over the years.
To the patients who enrich my life by entrusting me to care for them, thank you for your strength despite adversity, vulnerability, and willingness to embark on a journey of healing with me.

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Preface

The *Practical Management of Pain*, first published in 1986, is one of the established textbooks on pain management. In 2008, several of the current editors took over editorial leadership of the fourth edition of the book. As pain is multidimensional, starting in the fourth edition and continuing in the present edition, we the editors, represent several disciplines related to pain: anesthesiology, neurology, and psychology.

The *Practical Management of Pain* has evolved due to our increasing understanding of pain and its underlying mechanisms, which is reflected throughout this volume. Topics such as local anesthetics, neuraxial anesthesia, technique of peripheral nerve blocks, and associated topics were discontinued to focus on pain-related topics. In this updated and expanded edition, we have enlisted an outstanding set of clinicians and researchers with considerable expertise in all facets of pain and its management to provide contemporary information as to why and how best to evaluate and treat patients experiencing pain. We believe that this volume truly represents state-of-the-art knowledge and understanding of pain and its management.

To represent the growing body of knowledge in the field, we have added Andrea Chadwick to this edition. Dr. Chadwick brings particular expertise in the areas of fibromyalgia, non-opioid management of pain, radiation exposure, among other topics.

The production of a textbook involves the contributions, encouragement, and support of a number of people. We thank the authors, Michael Houston, Lisa Barnes, Manikandan Chandrasekaran, Baljinder Kaur of Aptara, and everyone related to the development of this edition.

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1

History Is a Distillation of Rumor

NATALIE MORYL, CHARLES INTURRISI

THOMAS CARLYLE (1795-1881)

Management of pain, such as the management of any disease, is as old as the human race. In the view of Christians, the fall of Adam and Eve in the Garden of Eden produced a long life of suffering pain for men and women. This act allegedly sets the stage for several disease concepts, including the experience of pain in labor and delivery, the concept that hard work is painful, the notion that blood, sweat, and tears are needed to produce fruit; *the introduction of pain and disease to human existence*; establishment of the fact that hell and its fires are painful; and the expectation that heaven is pure, delightful, spiritually pleasing, and of course, pain free. From a historical perspective, humans have deliberately and knowingly inflicted on one another many experiences associated with pain—from the earliest wars to the more recent irrational shooting incidents in Sandy Hook Elementary School in Newtown, Connecticut, and Marjory Stoneman Douglas High School in Parkland, Dallas from the scourging of Jesus to contemporary strife in the Middle East, the Rwandan genocide, the Irish "religious" fratricide, and the conflicts in Bosnia and the Balkans. All wars, including the great wars, World War I and World War II, the American Civil War, the Korean War, and the Vietnam War, have been associated with untold pain, suffering, and death.

In these concepts, pain is viewed as a negative experience and one that is associated with disease and death. Many diseases, including infections, plagues, and genetic and acquired disorders, including cancer and COVID-19, can cause significant pain. In contrast to acute pain that may teach us a lesson, that is, we would not touch a hot stove the second time after the initial touch brings sharp short-lived pain, chronic pain offers no such benefits. It interferes with our quality of life, sleep, work, and enjoyment of life and often causes anxiety, depression, and decreased mobility, which may precipitate or worsen other medical conditions resulting from inactivity. Most recently, social media has created a platform for those who may ordinarily suffer in silence the freedom to share and open up about their suffering and pain. Social media has become a powerful tool for people with pain to share their stories and reach new audiences across the globe, creating new patient communities. This has empowered patients with pain to set up new expectations during treatment of conditions commonly associated with pain, such as cancer, diabetes, HIV, and others.

Medical and technological advances in the 21st century have changed the outcomes of many diseases and the probability of survivorship. Cultural and religious changes in many societies have also changed the way patients view the disease. Various advocacy groups have empowered patients and caregivers to change what is viewed as acceptable during various treatments. Patients' experience has been gaining priority not only for patients but also for research, clinicians, and the medical system overall. Originally conceived in 2001 by the National Institutes of Health, the patient-reported outcomes measurement information system (PROMIS) has involved hundreds of medical researchers and psychometricians and received approximately $250 million in funding.[1,2] Further research showed that not only patients wanted to drive communications by reporting their distress with pain and other symptoms, but both caregivers and clinicians found regular communications from the patient reporting pain and other symptoms useful for clinical care.

This chapter focuses on some of the major historical events that have led to the current conceptualization of pain and its treatment as an independent specialty in modern medicine.

Pain and Religion

The early concept of pain as a form of punishment from supreme spiritual beings for sin and evil activity is as old as the human race. In the book of *Genesis*, God told Eve that following her fall from grace, she would endure pain during childbirth: "I will greatly multiply your pain in childbearing; in pain you shall bring forth children, yet your desire shall be for your husband, and he shall rule over you" (Genesis 3:16). This condemnation led early Christians to accept pain as a normal consequence of Eve's action and to view this consequence as being directly transferred to them. Thus any attempt to decrease the pain associated with labor and delivery was treated by early Christians with disapproval and disapproval. It was not until 1847, when Queen Victoria was administered chloroform by James Simpson for the delivery of her eighth child, Prince Leopold, that contemporary Christians and, in particular, Protestants accepted the notion that it was not heretical to promote painless childbirth as part of the obstetric process.

From the Old Testament, Job has been praised for his endurance of pain and suffering. While Job's friends wondered whether these tribulations were an indication that he had committed some great sin for which God was punishing him (Job x:17), Job was considered a faithful servant by God, not guilty of any wrongdoing. He was described as a man who was "blameless and upright" and one who feared God and turned away from evil.[3]

In the 5th century, St. Augustine wrote that "all diseases of Christians are to be ascribed to demons; chiefly do they torment the fresh baptized, yea, even the guiltless newborn infant," thus implying that not even innocent infants escape the work of demons. In the 1st century, many Christians were rebuked and

suffered ruthless persecution, including death, because of their belief in Jesus as the Messiah. Some who were subsequently described as martyrs endured their suffering in the belief that they did it for the love of Christ, and they felt that their suffering identified them with Christ's suffering on the cross during his crucifixion.[4] This may be the earliest example of the value of psychotherapy as an important modality in managing pain. Thus some present-day cancer patients with strong religious beliefs view their pain and suffering as part of their journey toward eternal salvation. This concept has led to several scientifically conducted and government-sponsored studies evaluating intercessory prayer as an effective modality for controlling cancer pain.

To fully appreciate the historical concept of pain, it is important to reflect on the origins of the term "pain patient." The word *pain* comes from the Latin word *poena*, which means that "punishment." The word *patient* is derived from the Latin word *patior*, meaning "to endure suffering or pain." Thus it is not too outrageous to appreciate that in ancient days persons who experienced pain were interpreted to have received punishment in the form of suffering that was either dispensed by the gods or offered up to appease the gods for transgressions.[5,6]

In some cultures, the tribal concept of pain came from the belief that it resulted from an "intrusion" from outside the body. These "intruders" were thought to be evil spirits sent by the gods as a form of punishment. In this setting, the role of medicine men and shamans flourished because these were the persons assigned to treat the pain syndromes associated with internal disease. Since it was thought that spirits entered the body by different avenues, the rational approach to therapy was aimed at blocking the particular pathway chosen by the spirit.

In Egypt, the left nostril was considered to be the specific site where the disease entered. This belief was confirmed by Papyri and Berlin, who stated that the treatment of headache involved expulsion of the offending spirit by sneezing, sweating, vomiting, urination, and even trephination.[7,8] In New Guinea, it was believed that evil spirits entered via a spear or an arrow, which then produced spontaneous pain.[7] Thus it was common for the shaman to occasionally purge the evil spirit from a painful offending wound and neutralize it with his special powers or special medicines. Egyptians treat some forms of pain by placing an electric fish from the Nile over the wounds to control pain.[8,9] The resulting electrical stimulation that produced relief of pain actually works by a mechanism similar to transcutaneous electrical nerve stimulation (TENS), which is frequently used today to treat pain. The Papyrus of Ebers, an ancient Egyptian manuscript, contains a wide variety of pharmacologic information and describes many techniques and recipes, some of which still have validity.[8,9]

Early Native Americans believed that pain was experienced in the heart, whereas the Chinese and India identified multiple points in the body where pain might originate or might be self-perpetuating.[10] Consequently, attempts were made to drain the body of these "pain points" by inserting needles, a concept that may have given birth to the principles of acupuncture therapy, which is well over 2000 years old.[11]

The ancient Greeks were the first to consider pain to be a sensory function that might be derived from peripheral stimulation.[12] In particular, Aristotle believed that pain was a central sensation arising from some form of stimulation of the flesh, whereas Plato hypothesized that the brain was the destination of all peripheral stimulation. Aristotle advanced the notion that the heart was the origin or processing center for pain. He based his hypothesis on the concept that an excess of vital heat was conducted by the blood to the heart, where pain was modulated and perceived. Because of his great reputation, many Greek philosophers followed Aristotle and embraced the notion that the heart was the center for pain processing.[13] In contrast, another Greek philosopher, Stratton, and other distinguished Egyptians, including Herophilus and Eistratus, disagreed with Aristotle and proposed the concept that the brain was the site of pain perception, as suggested by Plato. Their theories were reinforced by actual anatomic studies showing the connections between the peripheral and central nervous systems.[14]

Nevertheless, controversies between the opposing theories of the brain and the heart as the center for pain continued. It was not until 400 years later that the Roman philosopher Galen rejuvenated the works of the Egyptians Herophilus and Eistratus and greatly re-emphasized the model of the central nervous system. Although Galen's work was compelling, he received little recognition until the 20th century.

Toward the period of the Roman Empire, steady progress was made in understanding pain as a sensation similar to other sensations in the body. Developments in anatomy and, to a lesser extent, in physiology helped establish that the brain, not the heart, was the center for the processing of pain.[15] While these advances were taking place, simultaneous advances were occurring in the development of therapeutic modalities, including the use of drugs (e.g. opium), as well as heat, cold, massage, trephination, and exercise, to treat painful illnesses. These developments led to the establishment of the principles of surgery for treating diseases. Electricity was first used by the Greeks of that era, as they exploited the power of the electrogenic torpedo fish (*Scribonius longus*) to treat the pain of arthritis and headache. Electrostatic generators, such as the Leyden jar, were used in the late Middle Ages, resulting in the re-emergence of electrotherapy as a modality for managing medical problems, including pain. However, there was a relative standstill in the development of electrotherapy as a medical modality until the electric battery was invented in the 19th century. Several attempts have been made to revive its use as an effective medical modality, but these concepts did not catch on and were largely used only by charlatans and obscure scientists and practitioners.

Over the centuries, many modes of anesthesia/analgesia have been developed and refined so that their mortality and morbidity have become negligible. General anesthesia was formally discovered by William Morton in 1846. In 1847, while even the concept of analgesia for the relief of labor pain was considered heretical and unchristian, Simpson used chloroform to provide anesthesia for the labor pains of Queen Victoria during the delivery of her eighth child, Prince Leopold.[9] This action helped legitimize the practice of pain relief during childbirth. Around the same time, a hollow needle and syringe were invented. Many local anesthetic agents have been discovered in this era. In 1888, Corning described using a local anesthetic, cocaine, to treat nerve pain. Techniques for local and regional anesthesia for both surgery and pain disorders have proliferated rapidly.

The history of anesthesia is full of instances wherein attempts to relieve pain were initially met with resistance and sometimes violence. In the mid-19th century, Crawford Long from the state of Georgia in the United States attempted to develop and provide anesthesia, but contemporary Christians of that state considered him a heretic for his scholarly activity. As a result, he had to flee for his life from Georgia to Texas. Although surgical anesthesia was well-developed in the late 19th century, religious controversy over its use required Pope Pius XII to give his approval before anesthesia could be used extensively for surgical procedures.[6] Pope Pius XII wrote, "The patient, desirous of avoiding or relieving pain, may

without any disquietude of conscience, use the means discovered by science which in themselves are not immoral." More recently, the Church endorsed palliative care, including pain management using high-dose opioids or sedatives at the end of life (even if life-shortening) as long as the palliative therapies were proportionate and used to treat refractory symptoms in a terminally ill patient. Pope John Paul II stated: "Moreover, while patients in need of pain killers should not be made to forego the relief that they can bring, the dose should be effectively proportionate to the intensity of their pain and its treatment." (http://www.ldysinger.stjohnsem.edu/@magist/1978_JP2/Addresses/04_11_pal-care.htm).

Pain and Pain Theories

Throughout the Middle Ages and the Renaissance, the debate on the origin and processing center of pain raged. Fortunes fluctuated between proponents of the brain theory and proponents of the heart theory, depending on which theory was favored.

Heart theory proponents appeared to prosper when William Harvey, recognized for his discovery of the circulation, supported the heart as the focus for pain sensation. However, Descartes disagreed vehemently with the Harvey hypothesis, and his description of pain conducted from peripheral damage through nerves to the brain led to the first plausible pain theory, that is, the *specificity theory*.[16] In his 1664 Treatise of Man, René Descartes traced a pain pathway and described pain as "a specific sensation, with its own sensory apparatus independent of touch and other senses."

In the 1850s, by examining the effect of incisions in the spinal cord, Schiff[16] demonstrated that touch and pain were sensations independent of each other. He postulated that pain had its own specific nervous system pathways from the spinal cord that traveled to the brain. Further work along the same lines by Bliz,[17] Goldscheider,[18] and von Frey[19] contributed to the concept that separate and distinct receptors exist for the modalities of pain, touch, warmth, and cold.

During the 18th and 19th centuries, new inventions, new theories, and new thinking emerged. This period was known as the Scientific Revolution, and several important inventions took place, including the discovery of the analgesic properties of nitrous oxide, followed by the discovery of local anesthetic agents (e.g. cocaine). Anatomy has also developed rapidly as an important branch of science and medicine; most notably, the discovery of the anatomic division of the spinal cord into sensory (dorsal) and motor (ventral) divisions. In 1840 Mueller proposed that based on anatomic studies, there was a straight-through system of specific nerve energies in which specific energy from a given sensation was transmitted along sensory nerves to the brain.[20] Mueller's theories led Darwin to propose the intensive theory of pain,[21] which maintained that the sensation of pain was not a separate modality but instead resulted from a sensory overload of sufficient intensity for any modality. This theory was modified by Erb[22] and then expanded by Goldscheider[18] to encompass the roles of both stimulus intensity and central summation of stimuli. Although the intensive theory was persuasive, the controversy continued, with the result that by the mid-20th century, the specificity theory was universally accepted as the more plausible theory of pain.

With this official, though not unanimous blessing of the contemporary scientific community, strategies for pain therapy began to focus on identifying and interrupting pain pathways. This tendency was both a blessing and a curse. It was a blessing in that it led many researchers to explore surgical techniques that might interrupt pain pathways and consequently relieve pain, but it was a curse in that it biased the medical community for more than half a century into believing that pain pathways and their interruption were the total answer to the pain puzzle. This trend began in the late 19th century by Letievant, who first described specific neurectomy techniques for treating neuralgic pain.[23] Afterward various surgical interventions for chronic pain were developed and used, including rhizotomy, cordotomy, leukotomy, tractotomy, myelotomy, and several other operative procedures designed to interrupt the central nervous system and consequently reduce pain.[24] Most of these techniques were abysmal failures that did not relieve pain and occasionally resulted in more pain than previously present.

Pain as a Disease

The cardinal features of disease as recognized by early philosophers included calor, rubor, tumor, and dolor. The English translation is heat, redness, swelling, and pain. One of the important highlights in the history of pain medicine was the realization that even though heat, redness, and swelling may disappear, pain can continue and be unresponsive on occasion to different therapeutic modalities. When pain persists long after the natural pathogenic course of disease has ended, a chronic pain syndrome develops with characteristic clinical features, including depression, disability, disuse, and decreased mobility, causing other medical conditions such as obesity and arthritis to worsen. The risk of another comorbidity of chronic pain increases with chronic opioid exposure that, in some instances, can be complicated by dependency and opioid use disorder, formally known as addiction. John Dryden once wrote, "For all the happiness mankind can gain is not in pleasure, but in rest from pain." Thus many fatal nonpainful diseases are not as feared as relatively trivial, painful ones.

Physicians and healers have focused their attention on managing pain. Thus in managing cancer, an important measure of successful treatment is the success with which any associated pain is managed. Although many technological advances have been made in medicine, it is only within the past 10 to 20 years that significant strides have been made in dealing with chronic pain as a disease entity per se—one requiring specialized assessment, workup, diagnosis, and specialized therapeutic interventions targeting the cause of pain and pain itself.

Pain in the 20th Century

In 1907, Schlosser reported significant relief of neuropathic pain for long periods with the injection of alcohol into damaged and painful nerves. Reports of similar treatment came from the management of pain resulting from tuberculous and neoplastic invasion.[25] In 1926 and 1928, Swetlow and White, respectively, reported on the use of alcohol injections into thoracic sympathetic ganglia to treat chronic angina. In 1931, Dogliotti described the injection of alcohol into the cervical subarachnoid space to treat pain associated with cancer.[26]

One consequence of war has been the development of new techniques and procedures to manage injuries. During World War I (1914-1918), numerous injuries were associated with trauma (e.g. dismemberment, peripheral vascular insufficiency, and frostbite). In World War II (1939-1946), peripheral vascular injuries as well as phantom limb phenomena, causalgia, and many sympathetically mediated pain syndromes occurred. Leriche developed the technique of sympathetic neural blockade with procaine to treat the causalgic injuries of war.[27] John Bonica, himself an army surgeon during World War II, recognized the gross inadequacy of

managing war injuries and other painful states of veterans with the existing uni-disciplinary approaches.[28] This led him to propose the concept of multi-disciplinary, multimodal management of chronic pain, including behavioral evaluation and treatment. Bonica also highlighted the fact that all kinds of pain were being undertreated; his work has borne fruit in that he is universally considered the "father of pain," and he was the catalyst for the formation of many established national and international pain organizations. Bonica's lasting legacy is his historic volume *The Management of Pain*, first published in 1953. The clinic that he developed at the University of Washington in Seattle remains a model for the multi-disciplinary management of chronic pain. As a result of his work, the American Pain Society (APS) and the International Association for the Study of Pain (IASP) were formed. Anesthesiology was developed as a division of surgery and did not reach full autonomy until after World War II. With the discovery of new local anesthetics, regional anesthesia began to flourish in the United States. Bonica's wife had a very difficult delivery, alerting Dr. Bonica to the gap in childbirth analgesia. He played a major role in advancing the safe use of epidural anesthesia to manage the pain associated with labor and delivery in the 20th century. Regional anesthesia suffered a significant setback in the United Kingdom with negative publicity surrounding the 1954 cases of Wooley and Roe, in whom serious and irreversible neurological damage occurred after spinal anesthesia. It took three more decades to fully overcome this setback and to see regional anesthesia widely accepted as safe and effective in the United Kingdom. Several persons contributed significantly to the development of regional anesthesia, including Corning, Quincke-August Bier, Pitkin, Etherington-Wilson, Barker, and Adriani.

An outstanding contribution in the field of research was the development and publication of the *gate control theory* by Melzack and Wall in 1965.[29] This theory, which was built on the preexisting and prevalent specificity and intensive theories of pain, provided a sound scientific basis for understanding pain mechanisms and for developing other concepts on which sound hypotheses could be developed. The gate control theory emphasizes the importance of both ascending and descending modulation systems and provides a solid framework for the management of different pain syndromes. The gate control theory almost single-handedly legitimized pain as a scientific discipline and led not only to many other research endeavors building on the theory but also to the maturity of pain medicine as a science.[30] As a consequence, the American Academy of Pain Medicine (AAPM), the American Society of Regional Anesthesia and Pain Medicine, the IASP, and the World Institute of Pain (WIP) have become serious and responsible organizations that deal with various aspects of pain medicine, including education, science, certification, and credentialing of members of the specialty of pain medicine.

Dr. Jan Sternsward, Chief of the Cancer Unit at the World Health Organization (WHO), collaborated with IASP to focus on cancer pain and palliative care for cancer patients worldwide. In 1982, representatives from IASP, including Drs. Mark Swerdlow, John Bonica, Robert Twycross, Kathleen Foley, and Fumi Takeda met in Italy and developed what eventually became the 1986 report entitled cancer pain relief. With IASP, WHO made a historic statement declaring pain relief a human right issue and called on member states to make pain-relieving drugs available, including oral morphine, which was on the WHO essential drug list.

Memorial Sloan Kettering's James Ewing Hospital (MSK) was a focal point for the main site to evaluate new analgesics in patients with cancer pain. A young internist, Dr. Raymond Houde, with the assistance of a research nurse, Ada Rogers, and a psychologist, Stanley Wallenstein, began work on opioid pharmacology, including equianalgesic opioid doses in 1951. From Henry Beecher at Harvard and from his own experiments with student volunteers at Michigan, he learned that the perception of pain was modified by multiple variables—emotional state, expectations or fears for the future, previous medications or treatments, and the course of the disease itself. Houde's meticulous and patient-sensitive methods were recognized in the late 1950s as the standard for analgesic trials. A neurologist, Kathleen Foley, brought together various programs to form the first designated pain service in a cancer setting in the United States. In addition to Dr. Houde and Ada Rogers, it included Charles Inturrisi, professor of pharmacology at Weill Cornell Medical College, and Gavril Pasternak, professor of neurology, who was developing a laboratory to study opiate receptors in the brain. This program combined basic and clinical research, along with a training program as well as a supportive care program for patients with complicated pain started by a PhD nurse practitioner, Nessa Coyle. Dr. Kathleen Foley published the first taxonomy of cancer pain syndromes.

Pain and the Impact of Psychology

The history of pain medicine is incomplete without acknowledging the noteworthy contributions of psychologists. Their influential research and clinical activities have been an integral part of a revolution in the conceptualization of the pain experience.[31] For example, in the early 20th century, the role of the cerebral cortex in the perception of pain was controversial because of a lack of understanding of the neuroanatomic pathways and the neurophysiologic mechanisms involved in pain perception.[32,33] This controversy largely ended with the introduction of the gate control theory by Wall and Melzack in 1965.[29] The gate control theory has stood the test of time in subsequent research using modern brain-imaging techniques such as positron emission tomography, functional magnetic resonance imaging, and single-photon emission computed tomography have also described the activation of multiple cortical and subcortical sites of activity in the brain during pain perception. Further elaboration of the psychological aspects of the pain experience includes the three psychological dimensions of pain: sensory-discriminative, motivational-affective, and cognitive-evaluative.[34]

Psychological researchers have greatly advanced the field of pain medicine by reconceptualizing both the etiology of pain experience and treatment strategy. Early pain researchers conceptualized pain experience as a product of either somatic pathology or psychological factors. However, psychological researchers have convincingly challenged this misconception by presenting research that illustrates the complex interaction between biomedical and psychosocial factors.[35–37]

This biopsychosocial approach to pain encourages the realization that pain is a complex perceptual experience modulated by a wide range of biopsychosocial factors, including emotions, social and environmental contexts, and cultural background, as well as beliefs, attitudes, and expectations. As the acutely painful experience transitions into a chronic phenomenon, these biopsychosocial abnormalities develop permanency. Thus chronic pain affects all facets of a person's functional universe at great expense to the individual and society. Consequently, logic dictates that this multimodal etiology of pain requires a multimodal therapeutic strategy for optimal cost-effective treatment outcomes.[38,39]

Additional contributions from the field of psychology include therapeutic behavioral modification techniques for pain

management. Techniques such as cognitive behavioral intervention, guided imagery, biofeedback, and autogenic training are the direct results of using the concepts presented in the gate control theory. In addition, neuromodulatory therapeutic modalities such as TENS, peripheral nerve stimulation, spinal cord stimulation, and deep brain stimulation are also logical offspring of the concepts presented in the gate control theory.

The evaluation of candidates for interventional medical procedures is another valuable historical contribution from the field of psychology. Not only is the psychologist's expertise in the identification of appropriate patients valuable for the success of therapeutic procedural interventions for the management of pain, but the psychologist's expertise is also helpful in identifying patients who are not appropriate candidates for procedural interventions. Thus psychologists have contributed positively to the cost effectiveness and utility of diagnostic and therapeutic pain medicine. Psychologists' contribution to the care of patients with cancer pain is invaluable. Psychological research in cancer led by Dr. Jimmie Holland et al., MSK led to the development of a new field of psycho-oncology that is essential in addressing the pain and suffering of patients with cancer pain.

Pain and Pain Organizations

World Health Organization (WHO)

When diplomats met to form the United Nations in 1945, one of the things they discussed was the establishment of a global health organization. A year later, in New York, the International Health Conference in New York approved the Constitution of the WHO. In 1986, the WHO published the first analgesia step ladder and a detailed report on cancer pain relief, highlighting the prevalence and assessment of cancer pain, its undertreatment, recommended therapeutic modalities, and the need to educate healthcare workers and the general public. Among the few countries, the United States was represented by Dr. John J. Bonica, President of the IASP, and Dr. Kathleen Foley, Chair of the Pain Service, Department of Neurology, Sloan Kettering Cancer Center in New York.

The International Association for the Study of Pain (IASP)

The IASP is the largest multi-disciplinary, international association in the field of pain. Founded in 1973 by John J. Bonica, MD, the IASP is a nonprofit professional organization dedicated to furthering research on pain and improving the care of patients experiencing pain. Membership is open to scientists, physicians, dentists, psychologists, nurses, physical therapists, and other health professionals actively engaged in pain and to those who have a special interest in the diagnosis and treatment of pain. The IASP has members of more than 100 national chapters.

The goals and objectives of the IASP are to foster and encourage research on pain mechanisms and pain syndromes and improve the management of clinical pain. One of the instruments used to disseminate new information is the journal *Pain*. In addition, the IASP promotes and sponsors a highly successful biennial world congress, as well as other meetings. The IASP encourages the development of national chapters for the national implementation of the IASP's international mission. In addition, the IASP encourages the adoption of a uniform classification, nomenclature, and definition of pain and pain syndromes.

Special interest groups within the IASP include pain in children, neuropathic pain, herbal medicine, and cancer pain. The IASP also promotes and administers chronic pain fellowship programs for deserving candidates worldwide.

The American Pain Society (APS)

Spurred by the burgeoning public interest in pain management and research, as well as by the formation of the Eastern and Western United States Chapters of the IASP, the APS was formed in 1977 as a result of a meeting of the Ad Hoc Advisory Committee on the Formation of a National Pain Organization. Its main function was to carry out the mission of the IASP at a national level through interprofessional collaborations between basic and clinical pain researchers and clinicians. APS was dissolved in 2019 through Chapter 7 bankruptcy resulting from the OxyContin scandal. APS maintains that it was another victim of the opioid crisis after being "named a defendant in numerous spurious lawsuits related to opioids prescribing and abuse" Although APS has been dissolved, its journal, *the Journal of Pain*, continues independent of the APS that originated it. The United States Association for the Study of Pain is a new professional society for United States-based pain researchers.

Commission on the Accreditation of Rehabilitation Facilities

In 1983, the Commission on Accreditation of Rehabilitation Facilities (CARF) was the first to offer a system of accreditation for pain clinics and pain treatment centers. The CARF model was based on a rehabilitation system that emphasized both physical and psychosocial rehabilitation of patients suffering from pain. CARF promoted multi-disciplinary pain management programs offering not only medical but also mandatory psychological and physical therapy modalities for the management of pain. Its major goals included objective measures such as increased physical function, reduced intake of medication, and return-to-work issues.

The American Academy of Pain Medicine (AAPM)

AAPM was formed in 1983 at a meeting of the APS in Washington, DC, when a group of physicians formed a separate American Academy of Algology, later renamed the AAPM. Their goal was to address the deficiency in evaluating pain physicians' competence by creating uniform standards for training and credentialing. AAPM sponsored the American College of Pain Medicine, which organized, developed, and administered the first credentialing examination in 1992. The American College of Pain Medicine is not now called the American Board of Pain Medicine (ABPM). The goals of the AAPM include the promotion of quality care through research, education, and reimbursement. *The Clinical Journal of Pain*, the initial journal of the AAPM, is not affiliated with any pain medicine society. The AAPMs present journal is *Pain Medicine.* Both journals are well-respected.

The American Society of Regional Anesthesia and Pain Medicine (ASRA)

ASRA is the largest subspecialty medical society in anesthesiology and the leader in regional anesthesia and acute and chronic pain medicine. The society is based in the United States; other societies on regional anesthesia are based in Europe, Asia, and

Latin America. The international societies of regional anesthesia have changed the name of their highly cited journal, *Regional Anesthesia*, to *Regional Anesthesia and Pain Medicine*.

The American Society of Interventional Pain Physicians (ASIPP)

ASIPP is a national organization that represents the interests of interventional pain physicians. The society was founded in 1998 by Dr. L. Manchikanti and associates to improve the delivery of interventional pain management services in various settings, including hospitals, ambulatory surgical centers, and medical offices. ASIPP has become a successful advocate for the political and regulatory aspects of pain medicine. The ASIPP journal is indexed and called *Pain Physician*.

The American Academy of Hospice and Palliative Medicine (AAHPM)

AAHPM was founded in 1988 as an Academy of Hospice Physicians, and in 1996 it changed its name to the AAHPM to reflect a goal of this organization to control pain and other symptoms not only at the end of life but throughout the disease trajectory, from diagnosis through survivorship or end of life. AAHPM works closely with the American Board of Hospice and Palliative Medicine and disseminates its research through affiliation with a well-established *Journal of Pain and Symptom Management*. The goals of the multi-disciplinary AAHPM include providing education and clinical practice standards, fostering research, and sponsoring public policy advocacy for the chronically and terminally ill and their families.

The American Academy of Orofacial Pain

The American Academy of Orofacial Pain (AAOP) is an organization of healthcare professionals dedicated to the alleviation of pain and suffering through education, research, and patient care in the field of orofacial pain and associated disorders. The AAOP goals include the establishment of acceptable criteria for the diagnosis and treatment of orofacial pain and temporomandibular disorders, sponsorship of research, and annual meetings. Their journal, together with the European, Asian, Australian, and New Zealand Academy of Orofacial Pain, is *the Journal of Oral and Facial Pain and Headache*.

The American Academy of Pain Management (AAP Management)

AAP Management was founded in 1988 and changed its name to the Academy of Integrative Pain Management (AIPM) in 2016. The AIPM has promoted an integrative, interdisciplinary model of pain management. The AIPM closed its operations in 2019.

American Society for Pain Management Nursing (ASPMN)

Founded in 1990, ASPMN is an organization of professional nurses dedicated to providing access to specialized care for patients experiencing pain, providing education to the public regarding self-advocacy for their pain needs, and providing a network for nurses working in the pain management field. The ASPMN Journal is *Pain Management Nursing*.

The International Headache Society (IHS)

The International Headache Society is based in London. Its leadership is worldwide and is known for their international classification of headache disorders, now in its third edition. Another notable guideline is their International Classification of Orofacial Pain. In addition, their journal, *Cephalalgia*, has a fairly high impact factor.

The World Institute of Pain (WIP)

The WIP is an international organization that aims to promote the best practice of pain medicine throughout the world through training via international seminars and exchange of clinicians and education via newsletters, scientific seminars, and publications. One of the most important initiatives if the WIP is to develop an international examination process to certify qualified interventional pain physicians. After showing proficiency in both general pain knowledge and safe performance of interventional procedures, successful candidates are awarded the designation of *Fellow of Interventional Pain Practice* (FIPP). In addition, the journal of the WIP, *Pain Practice*, is indexed and has a very respectable impact factor.

The Spine Intervention Society (SIS)

The SIS, formerly called the International Spine Injection Society, is known for its leadership in interventional pain medicine. Their landmark monograph, *Practice Guidelines for Spinal Diagnostic and Treatment Procedures,* is the gold standard for spine interventions. Together with the AAPM, their journal is *Pain Medicine*.

The International Neuromodulation Society (INS)

Founded in 1989, INS is a unique multi-disciplinary, international society that consists of not only clinicians and scientists but also engineers dedicated to the scientific development and awareness of neuromodulation – the alteration of nerve activity through the delivery of electromagnetic stimulation or chemical agents to targeted sites of the body. The INS promotes the field through meetings and its journal *Neuromodulation*.

American Pain Foundation (APF)

Founded in 1997 by the APS (see above for the current status of APS), APF was the first pain organization specifically formed to serve the interests of people with diverse disorders associated with the presence of significant pain. Its goals include patient education, promoting recognition of pain as a critical health issue, and patient access to proper medical care. Regrettably, the organization dissolved in early 2012 because of financial difficulties.

International Association of Hospice and Palliative Care (IAHPC))

IAHPC was founded in 1980. From this, the Academy of Hospice Physicians grew. Two new independent organizations were formed: the AAHPM and the International Hospice Institute and College. IAHPC serves as a global platform to inspire, inform, and empower individuals, governments, and organizations to increase access and optimize the practice of palliative care.

The Worldwide Hospice Palliative Care Alliance (WHPCA)

WHPCA is an international non-governmental organization that includes members from over 100 countries, focusing exclusively on hospice and palliative care development worldwide.

International Children's Palliative Care Network (ICPCN)

The ICPCN is the only global organization working to improve access to palliative care for children. The ICPCN is recognized globally for its leadership, a wealth of educational resources, and a network of members in over 120 countries.

Pain and the Hospice Movement

Hospice is a medieval term representing a welcome place of rest for pilgrims to the Holy Land. The concept of hospice dates back to the reign of Emperor Julian the Apostate, when Fabiola, a Roman matron, created a place for sick and healthy travelers and cared for the dying.[40] In general, hospitals were regarded as Christian institutions, and in medieval times most hospitals were used as hospices and vice versa.[41]

The 17th century Catholic priest St. Vincent DePaul founded the Sisters of Charity in Paris as a home for the poor, the sick, and the dying. The movement grew, and the Protestant pastor Fliedner founded Kaiserwerth 100 years later. Nuns from both Sisters of Charity and Kaiserwerth accompanied Florence Nightingale to Crimea to care for wounded soldiers.[42]

In 1902, the Irish Sisters of Charity founded St. Joseph's hospice. Fifty years later, Cecily Saunders became the founder and medical director of St. Christopher's Hospice in England. She was initially trained as a nurse and served during World War II. After becoming injured, she received training as a social worker. She subsequently developed a keen interest in terminal cancer patients and underwent training in medical school to become a physician. She emphasized the importance of pain control at the end of life, believing patients' pain reports, the need for frequent pain assessments, and the scheduling of opioids for chronic pain instead of administering them on an as-needed basis.[43] For all her efforts and leadership, she is regarded as the "mother of palliative care" and was knighted for her contributions to the hospice movement and care of dying cancer patients. Dame Saunders' teachings are endorsed by medical and nursing schools today.

Pain and Palliative Care

Palliative care is a more recent specialty. The term palliative comes from Medieval Latin palliativus, "under cloak" or to cover, mitigate, or alleviate. Palliative care is provided to improve the quality of life of patients with serious or life-threatening diseases, such as cancer. The goal is to prevent or treat the symptoms and side effects of the disease as early as possible, in addition to any related psychological, social, and spiritual problems. Pain management, research, education, and advocacy are integral parts of palliative care.

Opioid Crisis

While trying to empower the patients to report pain and aiming at pain free outcomes of dental, surgical, and medical interventions and with pharma advertising directly to patients, opioid prescriptions and opioid overdoses started to increase, reaching the peak in 2017.[44] The first wave was from abuse of prescription opioids that was addressed by the Center for Disease Control and state and institutional guidelines.[45] Unfortunately, some of the patients with prescription opioid addiction went on to abuse street drugs, including heroin and illicit fentanyl.

Pharmaceutical companies, sued by several state attorney generals, agreed to a master settlement to defray the cost of the opioid crisis. As a result, the prescription of non-opioids has increased, and the search for non-opioid analgesics has become a priority for research and pharmaceutical companies. Access to the treatment of opioid addiction has become one of the priorities of the federal government, resulting in buprenorphine-naloxone medication-assisted addiction treatment available through primary care and other certified clinicians. This has become an alternative to methadone maintenance clinics that are much more easily accessible to patients. Since COVID-19, there has been an increase in opioid overdose deaths.

Pain and the Future

The contributions of the IASP, WIP, International Headache Society (IHS), AAPM, ASRA, ASIPP, and many other international, national, regional, state, and local organizations devoted to pain and pain management led to research, innovative techniques, new drug development, dissemination of knowledge, and local, national, and international networking. Pain practitioners and investigators are no longer isolated, and a flurry of published manuscripts and textbooks now cover a wide array of topics in pain medicine. Official credentialing is through the certificate of added qualification by the American Board of Anesthesiology. In addition, the WIP offers FIPP certification through examination. Some organizations are now offering certifications on basic knowledge and expertise in the use of ultrasound for interventional pain procedures.

Giving the patient's voice through patient-reported outcomes (PRO) and social networking led to new patient-healthcare provider relationships. Data on PROs and the increasing interest in cost effectiveness made it clear that the scientific community concerned with pain must develop reliable and reproducible outcome measures to maintain high quality, credibility, integrity, and competence in the management of pain.

Key Points

- The word *pain* comes from the Latin word *poena*, which means "punishment." The word *patient* is derived from the Latin word *patior*, meaning "to endure suffering or pain."
- The history of anesthesia is full of instances in which attempts to relieve pain were initially met with resistance and at times violence.
- Developments in anatomy and physiology helped establish that the brain, not the heart, was the center for processing pain.
- The tenet of the specificity theory, proposed by Descartes and revised by Schiff, was that each sensory modality, including pain, was transmitted along an independent pathway.

- The use of chloroform to provide anesthesia for the labor pains of Queen Victoria helped to legitimize the practice of pain relief during childbirth.
- The clinic that Bonica developed at the University of Washington in Seattle remains a model for the multi-disciplinary management of chronic pain.
- The pain program that was developed at the Memorial Sloan Kettering Cancer Center was the first cancer pain program to remain a model for multi-disciplinary pain and palliative care programs for management and research in cancer pain.
- An outstanding contribution in the field of research was the development and publication of the *gate control theory* by Melzack and Wall in 1965.
- Psychological researchers have greatly advanced the field of pain medicine by reconceptualizing both the etiology of pain experience and treatment strategy.
- Several organizations have advanced the science and practice of pain medicine, including the IASP, American Society of Regional Anesthesia and Pain Medicine, AAPM, ASIPP, WIP, SIS, IHS, and INS. Pain medicine practitioners are certified by the American Board of Anesthesiology and the ABPM.

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2

Classification of Acute Pain and Chronic Pain Syndromes

JUAN C. MORA, RENE PRZKORA, MATTHEW MERONEY

Definition of Pain

The International Association for the Study of Pain (IASP) updated the definition of pain in 2020. The previous definition remained unchanged for more than 40 years (originally released in 1979), but it provided a necessary and widely accepted description in the medical field. The 1979 definition of pain was as follows: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] One year later, with a better understanding of pain and new research, the IASP understood the necessity of modifying the definition. They created an expert task force comprising 14 members. After two years of discussion, the 2020 definition was updated to read: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[2] This new definition includes those unable to articulate their pain verbally, such as infants and the elderly.

It is also important to note a few items to make this definition complete:[2]

1. Pain is a personal experience influenced by biologic, psychological, and social factors.
2. Pain cannot be inferred solely from activity in sensory neurons or nociceptors.
3. Each individual will learn the concept of pain through life experiences.
4. The report of an experience of pain should be respected.
5. Despite having an important adaptive role, pain may have adverse effects on function and social and psychological well-being.
6. A verbal description is only one of several behaviors to express pain, and the inability to communicate does not negate the possibility of experiencing pain.

Taxonomy and Classification

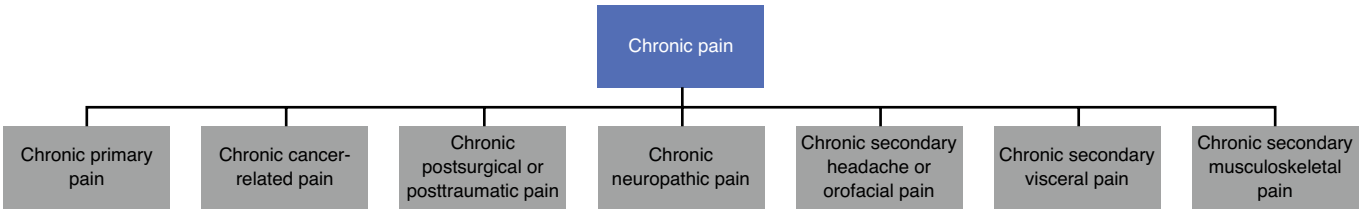
Taxonomy derives from the Greek words *tasso* (arrangement) and *nomia* (rules or law), and it is defined as an organization of concepts arranged using hierarchical relationships. The purpose of creating a medical classification is pragmatic and includes exchanging standardized information, facilitating statistical comparisons, and improving research at national and international levels.[3] An ideal classification should be comprehensive, biologically plausible, reliable, and exhaustive, and each item should be independent and mutually exclusive. However, achieving all of these can be challenging in medical taxonomy.[3]

Currently, there are multiple classifications, groupings, and descriptions of different medical disciplines. Perhaps the most well known is the International Classification of Diseases (ICD), which includes multiple diagnoses and is used worldwide. Classifications related to pain have also been developed. Currently, there is a classification for psychiatric conditions that can be found in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, fifth edition (V). The categorization of headaches can be found in the International Classification of Headache Disorders. The classification for acute pain can be found in the ACTTION-APS-AAPM Acute Pain Taxonomy (see Section E, Acute Pain, for more on this workgroup). The classification of chronic pain was provided by the IASP.

International Classification of Diseases (ICD)

In 1793, Dr. Francois Bossier de Sauvages de Lacroix, a French physician and botanist, developed a categorization of 10 main pathologic conditions, subdivided into 2,400 unique diseases. This is believed to be the origin of the ICD.[4] In 1853, a plan was made to create a worldwide system for classifying causes of mortality during the International Statistical Congress. This work was completed in 1893 and named the "International List of Causes of Death." This list was adopted by multiple countries, including the United States, and was updated every decade until 1938. In 1948, it was renamed the ICD when the World Health Organization took over this classification system, expanding the list to include not only mortality but also morbidity.[4] The ICD-6 was the first version to include psychiatric disorders. Starting with the ICD-9 in 1977, the list included 4-digit-level categories and optional 5-digit subdivisions, resulting in a better level of detail. This was advanced in 1992 with the ICD-10 when an alphanumeric code was introduced, dramatically improving specificity and expanding it from 17,000 to approximately 155,000 codes.[4] In this version, the conditions were classified by causal agents, systems of the body, symptom pattern, and type of psychiatric illness.[3] The implementation of the ICD-10 in the United States was officially approved in 2015 with clinical modifications.

The 11th and newest version of the ICD was released in 2018 and approved by the World Health Assembly in 2019. With the contribution of an IASP taskforce, this version is considered more flexible than its predecessor. It has vast advantages in terms



• **Figure 2.1** International Classification of Diseases (ICD)-11 chronic pain terms.

of chronic pain definitions, given that in the past, this type of pain was associated with only a pathophysiologic mechanism, neglecting the psychological and social contributors.[5] In practical terms, chronic pain is still defined as pain that persists over three months.[5] An extremely relevant change is the differentiation of primary versus secondary pain syndromes, with the inclusion of the term "chronic primary pain." This term is intended to group several poorly understood conditions with the important component of emotional distress and/or significant functional disability not accounted for by other diagnoses.[5,6] Chronic pain would then be the parent code of seven children codes that comprise the most relevant groups of chronic pain conditions: chronic primary pain, chronic cancer-related pain, chronic postsurgical or post-traumatic pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain (Fig. 2.1).[5,6] These changes are promising to improve the acquisition of accurate epidemiologic data, provide adequate billing, and potentiate the development and implementation of new therapies for chronic pain conditions.

IASP Chronic Pain Classifications

The initial attempts to describe the taxonomy of chronic pain came from the IASP and were spearheaded by Dr. John Bonica[7] and Dr. Harol Merskey.[8] This was first published in 1986, followed by a modification in 1994 and subsequent small updates. The group defined the temporality of chronic pain as pain that has been present for more than six months.[8] Their classification method was based on a multiaxis approach, using the five main pain axes (Table 2.1). Combining various pain characteristics and the axes, which are signified by a specific number, would allow most existing pain syndromes to be represented by a five-digit code (Table 2.2).[8]

The first axis addresses the region (anatomic location) where the pain occurs and is chosen for practical purposes. Any chronic pain can be easily identifiable by the region of the body compared to identification by etiology, as the latter has proven very challenging and not always possible. Therefore the etiology was assigned to the last axis of the list.[9] The second axis represents the systems of the body that are involved in the pain (e.g., musculoskeletal, nervous, gastrointestinal) and provides the second digit of the code. The third axis describes the temporal characteristics of pain, with special attention to the pattern of occurrence (e.g., single episode, continuous, recurring, paroxysmal). The fourth axis deals with the patient's statement of intensity and is intended to capture the patient's own experience and report on the severity and duration of the pain. The fifth and last axes refer to the etiology of the pain and are possibly the ones with more challenges given the lack of understanding concerning the etiology of some painful conditions. It is not uncommon that this digit of the code is left unknown. At the end of this five-digit code, a letter can be added to increase the granularity of the taxonomy system. For example, the letter "a" could be added for acute, "s" for spinal pain, and "r" for radicular pain.[8]

TABLE 2.1 Pain Axes

Axis I	Regions
Axis II	Systems
Axis III	Temporal characteristics of pain: pattern of occurrence
Axis IV	Patient's statement of intensity
Axis V	Etiology

Acute Pain

This chapter would not be complete without addressing acute pain. The Acute Pain Medicine Shared Interest Group defines acute pain as "the physiologic response and experience to noxious stimuli that can become pathologic, is normally sudden in onset, time-limited, and motivates behaviors to avoid actual or potential tissue injuries."[10] It is part of the unavoidable core experiences and has been evolutionarily preserved to serve an essential role in protecting the host against multiple threats.[11] Timing differentiation between acute and chronic pain has had multiple definitions in the past, ranging from seven, 14, and 90 days to six months,[11–13] or when it persists past the normal time of healing.[7] However, there has to be an understanding that the transition from acute to chronic pain is a continuum, and they are not completely separate entities. Determining the cutoff time between the two could be very challenging and almost impossible.[11]

Most taxonomy attempts have been performed mainly for chronic pain. However, acute pain has not yet been fully considered. Classifications of acute pain were mainly unidimensional, focusing on sensory experience (pain intensity) and the use of different scales for its measurement.[11] Recent research has discussed that pain trajectories are an important concept and that there are multiple dimensions for acute pain.[11,14–16]

In 2016, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration, the American Pain Society (APS), and the American Academy of Pain Medicine (AAPM) collaborated to create the ACTTION-APS-AAPM Acute Pain Taxonomy, which provides a multidimensional classification for acute pain with five dimensions of pain, as described in Table 2.3. They also differentiate between acute pain as surgical/procedural (e.g., general surgery, dental surgery, orthopedic surgery) and nonsurgical

TABLE 2.2 IASP Axes with Codes

Axis I: Regions	
Head, face, and mouth	000
Cervical region	100
Upper shoulder and upper limbs	200
Thoracic region	300
Abdominal region	400
Lower back, lumbar spine, sacrum, and coccyx	500
Lower limbs	600
Pelvic region	700
Anal, perineal, and genital region	800
More than three major sites	900
Axis II: Systems	
Nervous system (central, peripheral, and autonomic) and special senses; physical disturbance or dysfunction	00
Nervous system (psychological and social)*	10
Respiratory and cardiovascular systems	20
Musculoskeletal system and connective tissue	30
Cutaneous and subcutaneous and associated glands (breast, apocrine, etc.)	40
Gastrointestinal system	50
Genito-urinary system	60
Other organs or viscera (e.g., thyroid, lymphatic, hemopoietic)	70
More than one system	80
Unknown	90
Axis III: Temporal Characteristics of Pain: Pattern of Occurrence	
Not recorded, not applicable, or not known	0
Single episode, limited duration	1
Continuous or nearly continuous, nonfluctuating	2
Continuous or nearly continuous, fluctuating severity	3
Recurring irregularly	4
Recurring regularly	5
Paroxysmal	6
Sustained with superimposed paroxysms	7
Other combinations	8
None of the above	9
Axis IV: Patient's Statement of Intensity: Time Since Onset of Pain	
Not recorded, not applicable, or not known	.0
Mild	
- One month or less	.1
Medium	
- One month to six months	.2
- More than six months	.3
- One month or less	.4
Severe	
- One month to six months	.5
- More than six months	.6
- One month or less	.7
- One month to six months	.8
- More than six months	.9
Axis V: Etiology	
Genetic or congenital disorders	.00
Trauma, operation, burns	.01
Infective, parasitic	.02
Inflammatory (no known infective agent), immune reactions	.03
Neoplasm	.04
Toxic, metabolic, radiation	.05
Degenerative, mechanical	.06
Dysfunctional (including psychophysiologic)	.07
Unknown or other	.08
Psychological origin (e.g., conversion hysteria)	.09

(e.g., neuropathic, ischemic, visceral, trauma, musculoskeletal), which allows physicians to identify conditions where it is possible to intervene before the onset of pain or tissue injury, potentially avoiding the progression to chronic pain.[11]

Headache Classification

The *International Classification of Headache Disorders* 3rd edition must be mentioned when evaluating headaches. This classification has created an orderly taxonomy of typically poorly classified neurologic diseases. The intuitive 1- to 5-digit classification code (Table 2.4) caters to general practitioners and headache specialists alike, and it allows for broad or specific diagnoses. The first digit determines the most general type of headache experienced by a patient. For example, (1) migraine, (2) tension-type headaches, and (3) trigeminal autonomic cephalalgias. More specific information leads to a more specific code: 1.2.3.1.1, which indicates familial hemiplegic migraine type 1.[17]

New Pain Classification

Efforts have been made to expand the descriptive factors of chronic pain. Until recently, pain was divided into nociceptive and neuropathic groups. Nociceptive pain is known as pain that

TABLE 2.3 ACTTION-APS-AAPM[a] Acute Pain Taxonomy Acute Pain Dimensions[11]

Dimensions	Description
#1: Core criteria	Specifies the inciting event, time from the event, and tissue involved.
#2: Common features	Characterizes the acute pain condition through common pain variables (symptoms, signs, quality).
#3: Modulating factors	Includes comorbidities (i.e., opioid tolerance) as well as sociodemographic, biopsychosocial, and surgical factors that may modulate the acute pain experience.
#4: Impact/functional consequences	Describes the recovery trajectory, including the interrelationship of the physical, social, psychologic, and vocational consequences resulting from the acute pain condition.
#5: Putative mechanisms	Includes the neurobiologic mechanisms related to the acute pain condition.

[a]*ACTTION*, analgesics, and addiction clinical trial translations, innovations, opportunities, and networks; *APS*, American Pain Society; *AAPM*, American Academy of Pain Medicine

TABLE 2.4 International Classification of Headache Disorders

1. Migraine
- **1.1 Migraine without aura**
- **1.2 Migraine with aura**
  - 1.2.1 Migraine with typical aura
    - 1.2.1.1 Typical aura with headache
    - 1.2.1.2 Typical aura without headache
  - 1.2.2 Migraine with brainstem aura
  - 1.2.3 Hemiplegic migraine
    - 1.2.3.1 Familial hemiplegic migraine (FHM)
      - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
      - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
      - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
      - 1.2.3.1.4 Familial hemiplegic migraine, other loci
    - 1.2.3.2 Sporadic hemiplegic migraine (SHM)
  - 1.2.4 Retinal migraine

From IHS Classification ICHD-3. Available at: https://ichd-3.org/1-migraine/. Accessed July 20, 2020.

arises from actual or threatened damage to non-neural tissue and is because of the activation of nociceptors, and neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.[18,19] A growing body of data has begun to show the need for a third descriptor of pain that occurs in patients who do not have acute tissue injury or signs of neuropathy.[20] The term "nociplastic pain" is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.[18,19] It has been created to describe dysfunction in nociceptive processing that results in hypersensitivity to seemingly normal sensations. Chronic pain conditions that demonstrate evidence of altered nociceptive processing may include fibromyalgia,[21] complex regional pain syndrome,[22] irritable bowel syndrome,[23] and visceral pain disorders,[24,25] among others. These efforts are meant to address pain that may frequently be classified as "pain of unknown origin," previously known as idiopathic pain. However, a distinction needs to be made that this new descriptor should be used when patients note altered nociception, and it would not be appropriate for a patient who notes pain without hypersensitivity. Critics of this new classification argue that nociceptive and neuropathic pain may be proven by the identification of damage to tissue or nervous structures. Proponents agree that no structural pathology accounts for the pain, but tests such as sensory testing,[22,25–29] sensory-evoked potentials,[30–32] and functional magnetic resonance imaging[21,25,33,34] support altered nociceptive processing.

Psychiatric Aspects of Chronic Pain

The diagnosis of chronic pain related to psychiatric disorders has recently been updated in the DSM-V. The DSM-IV contains somatization disorders, including hypochondriasis, pain disorder, and undifferentiated somatoform disorders that have been removed. These diagnoses were criticized because of their overlap and the resulting lack of clarity regarding the appropriate diagnosis. They required a specific number of complaints from four symptom categories and the need for somatic symptoms to be medically unexplained. The DSM-V replacement states that somatic symptom disorder encompasses somatic symptoms that create dysfunction or distress with significant thoughts, feelings, or behaviors focused on those symptoms for longer than six months. The requirement for medically unexplained symptoms was removed. Therefore the patient's symptoms may be related to other medical conditions. This change aimed to reduce the number of disorders a patient may be diagnosed with while making criteria more straightforward for non-psychiatric care physicians.[35]

The psychiatric aspects of chronic pain have evolved consistent with the changes in the DSM-V described above, psychiatric aspects of chronic pain have evolved. The focus on determining whether the patient's symptoms are medically unexplained, which in itself can be very challenging, has lessened, and more importance has been placed on symptoms. Generally, it is not recommended to give an individual a diagnosis of a mental disorder solely because a medical cause has yet to be established. This contrasts with previous methodologies that sought to categorize a patient's pain as related to a known medical problem versus a psychological origin, as noted in the DSM-IV. Several elements may contribute to somatic symptoms, including biologic vulnerability to increased pain,[20] traumatic experiences, and learned behaviors (care obtained from illness), as well as cultural practices that negatively brand psychological complaints compared to physical ones. Significant data have disproved the mind-body dualism view that the mind and body are distinct and separable. Patients who suffer from both pain and depression have been found to experience reduced physical, mental, and social functioning compared to patients with only depression or pain. Therefore treatments such as cognitive behavioral therapy for a patient with depression may have a significant impact on pain.[36] This being said, there are situations such as conversion disorder where it is possible to conclude that the patient's symptoms are not possible when considering medical pathophysiology.

International Psychiatric Classifications

There are two main entities in world psychiatric classification: the DSM, created by the American Psychiatric Association, and the ICD, created by the World Health Organization. Notably, the DSM is used mainly by psychiatrists in the United States, and the ICD system is used globally and is intended for use by all health practitioners. The ICD-10 classification of mental and behavioral disorders preserves parallel categories to those used in the DSM-V, although the descriptions are often different. However, the ICD-10 classification does not use the "checklist approach," but rather provides a general description and major criteria required.[35,37]

The ICD classification system has often been criticized for its representation of chronic pain.[6,38] Specifically, it has been claimed that the system allows for the documentation of chronic pain but lacks the ability to directly connect it to an additional (i.e., psychological) diagnosis that may be its cause. This could have the effect of confusing other medical providers who may think that the chronic pain condition is not associated with another separate condition. For example, pain because of known or inferred psychophysiologic mechanisms such as muscle tension pain or migraine, which is still believed to have a psychogenic cause, is coded under psychological or behavioral factors associated with disorders or diseases classified elsewhere (e.g. muscle tension pain or migraine). Musculoskeletal pain is organized according to anatomic sites but does not reference the underlying mechanism of pain.[38] The ICD-10 classification does provide a separate category of pain disorder, somatoform disorders F45.41 (pain disorder exclusively related to psychological factors). In essence, this category corresponds to what the DSM-V now calls somatic symptom disorders. In the ICD-10, the predominant complaint is persistent, severe, and distressing pain that cannot be explained fully by a physiologic process or a physical disorder.[37] The next iteration of the ICD, the 11th edition, to be released in 2022, has been created with the goal of further interconnectedness with DSM-V diagnoses to avoid a mismatch of mental pathologizing depending on which classification system is used.

In evaluating disability caused by pain for psychiatric purposes, one can reasonably apply the criteria of the World Health Organization Disability Assessment Schedule, version 2.0. This was created to evaluate a patient's ability to perform activities in six areas: understanding and communicating, getting around, self-care, getting along with people, life activities, and participation in society. This test is based on the International Classification of Functioning, Disability, and Health, and can be used for any medical condition. It may be useful for an initial evaluation to help guide intervention based on high scores in a certain domain or may be repeated to track progress. The World Health Organization Disability Assessment Schedule, version 2.0, is endorsed in the DSM-V and is meant to replace the global assessment of functioning scale previously mentioned in the DSM-IV, which was dropped because of concerns over a lack of clarity regarding symptoms, suicide risk, and disabilities.[35]

Key Points

- Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling, that associated with, actual or potential tissue damage."
- Taxonomy is the organization of concepts arranged using hierarchical relationships.
- The purpose of creating a medical classification is to exchange standardized information, facilitate statistical comparisons, and improve research at the national and international levels.
- Medical classifications also provide guidance for billing and reimbursement.
- Currently, multiple taxonomy systems classify medical conditions related to pain syndromes: ICD, chronic pain (IASP), ACTTION-APS-AAPM Acute Pain, DSM, and the International Classification of Headache Disorders.
- The ICD-10 is currently used worldwide, and the ICD-11 version is intended to be adopted in the near future.
- The IASP classification of chronic pain uses five axes: anatomic location, systems involved, temporal characteristics, intensity, and etiology.
- Pain can be described as nociceptive, neuropathic, and nociplastic.
- Nociplastic pain is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesion of the somatosensory system causing pain.

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3

Organizing an Inpatient Acute Pain Service

PREETMA KAUR KOONER, GREGORY W. TERMAN

The Rationale

Over the last decade, several surgical practices and public health initiatives, in addition to drug and technology advancements, have impacted inpatient acute pain services worldwide, for example, the continued development and implementation of less invasive surgical techniques, such as arthroscopy. Laparoscopy and robot-assisted surgery have reduced post-surgical pain and allowed nearly two-thirds of surgeries to be performed on an outpatient basis.[1] Nonetheless, moderate to severe pain is common after outpatient procedures as well,[2] and pain is still a leading cause of why patients scheduled for outpatient surgery are unable to go home and remain as inpatients. Indeed, the last minute consults stating that "pain is the only thing keeping [patient name] here" has become an increasingly common refrain. In short, even if outpatient surgery pain is treated effectively in an institution, inpatient post-surgical patients can be expected to have high levels of pain on average, as more patients and procedures are deemed suitable for outpatient surgery. This may explain why pain after inpatient surgery has shown only a marginal reduction in patients suffering from moderate to severe pain, dropping from 80% in 1995[3] to 65% in 2015[4]—despite an increase in inpatient pain services.

Post-operative pain management in both inpatient and outpatient settings has also been complicated by the dramatic increase in opioid-related morbidity and mortality from both illicit and prescribed opioids, which have occurred since the turn of the century (the so called "opioid crisis"). Sometimes conflicting regulatory, legislative, insurance, and institutional policies, largely aimed at outpatient opioid prescribing, have proven, at best, difficult to remember and, at worst, impediments to patient-centered post-operative pain care. Both primary care services and the patients they care for are often reluctant to use opioid analgesics for fear of side effects. In this regard, it is necessary to remember that ineffective post-operative pain management is also associated with a variety of medical and economic "side effects," including readmissions,[5] patient dissatisfaction with medical care,[6] possible transition to chronic pain,[7] and extended lengths of treatment (which has been associated with opioid use disorder diagnoses).[8] Moreover, with or without consistent evidence based policies and guidelines, achieving satisfactory acute pain management is challenging since patient post-operative analgesic requirements vary widely even following the same surgery. Several patient factors have been reported to influence post-operative opioid requirements, including:

- Preoperative pain sensitivity[9]
- Coexisting medical conditions and associated multiple drug administration[4]
- Pre-surgical opioid tolerance or history of drug abuse[10]
- Psychological factors, including catastrophizing, and anxiety[11,12]
- Age[13]
- Type of surgery[10]

Great care must be taken to consider all the characteristics mentioned above when deriving an analgesic plan for managing an individual's response to a surgical insult. Such careful acute pain management does not include opioids and has never been involved. The time is long past when acute or chronic pain caregivers should think of "opioid treatment" and "pain management" as synonyms. However, how can we explain how the 2001 "pain is the fifth vital sign" campaign has, in retrospect, been vilified as a plot to increase opioid prescribing? A "vital sign" implies assessment, not a particular treatment—just as a heart rate of 100 may be treated quite differently in a fetus *in utero* than in a cardiac cripple.

In summary, acute pain, if not pain in general, still suffers from a lack of careful assessment and functional goal-directed multimodal therapy. Despite repeated educational initiatives worldwide, including the International Association for the Study of Pain (IASP) *Global Year Against Acute Pain in 2011,* followed by the *Global Year Against Pain After Surgery in 2017,* and even the *Global Year of Prevention of Pain in 2020.* This chapter posits that investing in an inpatient-based acute pain service is still the best mechanism to ensure effective and safe acute pain care.

General Principles

The sequelae associated with acute pain, including surgical procedures, result from various components of the stress response, including cardiopulmonary, infectious, and thromboembolic complications, cerebral dysfunction, nausea and gastrointestinal paresis, fatigue, and prolonged convalescence. Throughout the process of organizing an acute pain program, it is helpful to remember the following statements:

- The post-operative pain management regimen should be designed with attention to providing patient comfort and

inhibiting nociceptive impulses sufficient to allow appropriate rehabilitation.

- A time-, energy-, and cost-effective acute pain program should optimally provide multimodal and multi-disciplinary interventions, including systemic and regional pharmacologic,[14] and non-pharmacologic treatments,[15,16] including stress reduction, transcutaneous electrical nerve stimulation, music therapy, and acupuncture.
- Surgical stress responses are inhibited most effectively by the neuraxial administration of local anesthetics, and the administration of other agents—systemically, neuraxially, or perineurally—contribute little additional reduction of the endocrine (metabolic and catabolic) stress response following operative procedures.[17,18]
- Parenteral opioids exaggerate the perioperative immune depression already triggered by the neuroendocrine response to surgery, although the clinical relevance of this observation is controversial.[19] Opioids administered into the epidural space have minor suppressive effects on surgically induced proinflammatory cytokines.[20]
- Effective analgesia can reduce post-operative morbidity and improve function. For example, thoracic epidural analgesia has been shown to improve post-operative spirometry and reduce pulmonary infections and atelectasis.[21,22]

The experience of a skilled anesthesiologist lends itself to providing leadership within an acute pain service. Anesthesiologists are proficient in the use of systemic and regional analgesic techniques, including peripheral and neuraxial nerve conduction blockade. They also often understand the surgical techniques and the insults that they impose and are frequently equipped with leadership skills for working within a multi-disciplinary team from their work in the operating room. Nonetheless, an anesthesiologist-based team is not the only service model. Nurse-based, anesthesiologist-supervised, inpatient acute pain services have also been demonstrated to provide safe and effective post-operative pain management.[23,24] Regardless of the service model, nursing involvement in an inpatient acute pain service is essential. Bedside nurses' impressions of a patient's analgesic needs and recovery is an invaluable element in the decision making process for any given patient, and because it is the nurse who will ultimately be delivering the care, nurses must understand the analgesic plan, goals, policies, and procedures that might pertain to their pain care.

Detailed practice guidelines and protocols can help streamline the ordering and implementation of patient care. Well-established protocols have been shown to reduce errors in realms outside pain management[25] and decrease the cost associated with prescribing choices.[26] At the University of Washington Medical Center, we have instituted multiple protocols, including order sets for patient-controlled analgesia (PCA), continuous and patient-administered epidural analgesia, ketamine and lidocaine infusions, and continuous perineural catheter infusions (Figs. 3.1-3.5). PCA and epidural analgesia protocols must include titration and bolus instructions to treat breakthrough or incident pain. Order sets should also include routine and specific monitoring orders, as well as treatment options for common and/or dangerous side effects (e.g. antiemetics and/or antipruritics, and opioid receptor antagonists to reverse respiratory depression). Ketamine, intravenous lidocaine, and perineural anesthetics are most frequently used as adjuncts to other analgesic therapies (e.g. PCA opioids and scheduled acetaminophen and/or nonsteroidal anti-inflammatory drugs). The recovery room, intensive care unit, and medical/surgical floor nurses must be trained to be familiar with the order set parameters. In most cases, nurses can autonomously assess patients and implement changes that successfully achieve adequate analgesia with minimal side effects.

An emerging area of concern for any anesthesiology-based pain service is the complexity of managing invasive pain management techniques (e.g. epidurals) in an era where an ever-increasing number of anticoagulants are given as treatment or prophylaxis for many medical and surgical indications. These indications include treatment of cardiac arrhythmias, valvular disease, and deep vein thrombosis prophylaxis. To aid in treating such patients with the least risk, the University of Washington Medical Center has designed institutional guidelines (based on national guidelines such as those of the American Society of Regional Anesthesia)[27] for the management of indwelling neuraxial and peripheral nerve catheters in patients treated concomitantly with anticoagulants (see Chapter 74). This document was designed to address the placement, maintenance, and removal of catheters in several common anticoagulation scenarios. The intention of such guidelines, which are linked to the electronic medical record, is to distill the existing scientific evidence and opinion into a format that is easy to access and apply in the patient care workflow.

Identifying Service Leadership

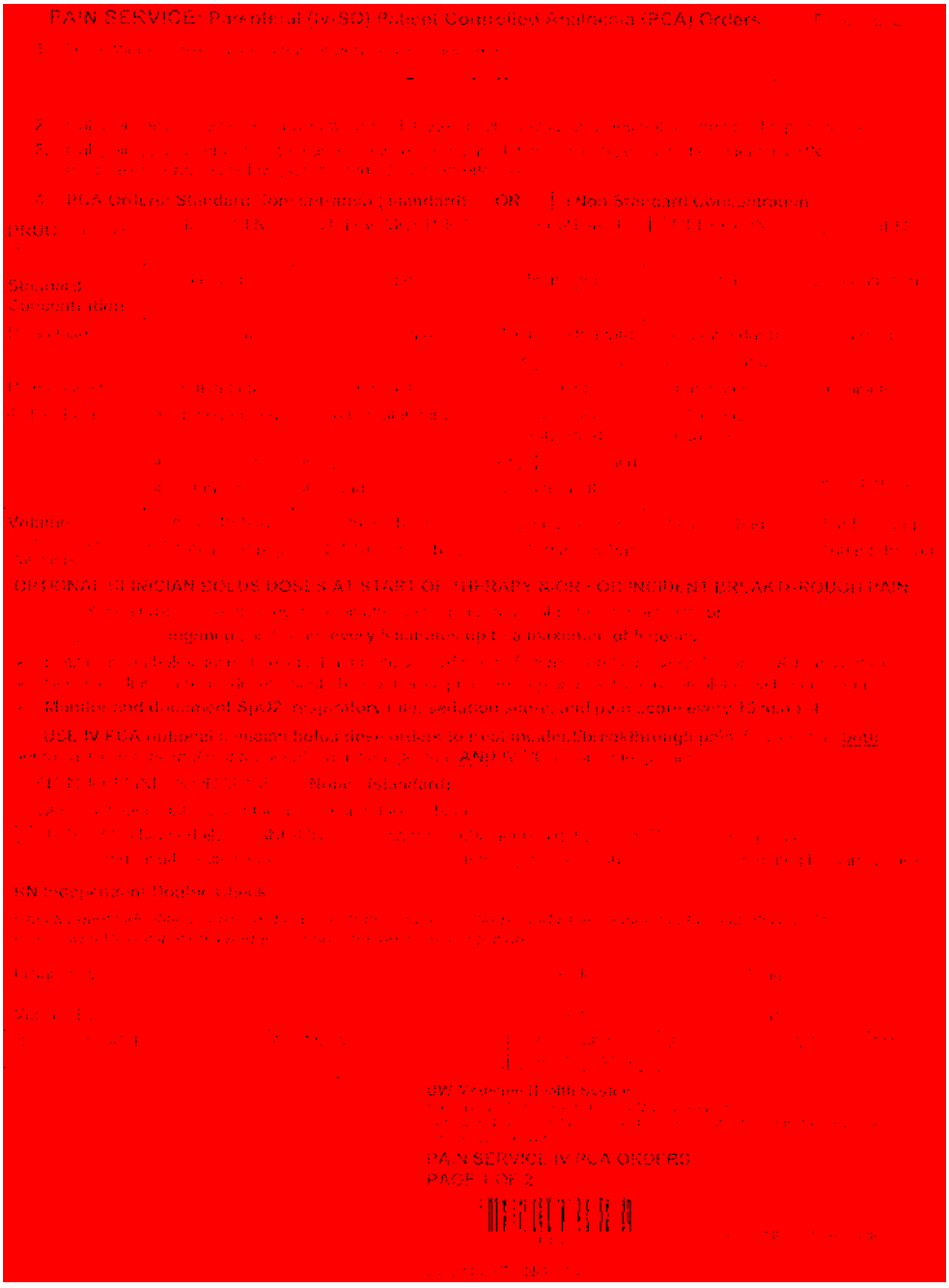
It is important to recognize at the outset of establishing a pain service that it is a major endeavor. Planning, design, and implementation of a successful service will require substantial human and material resources. If the need and desire for an acute pain service exist within a hospital facility, one must first elicit support from the anesthesiology department's chairperson. Although multiple design models for acute pain management services are possible, most will require that an anesthesiologist be made available for some level of participation in the service. Unless resources allow an anesthesiologist to be easily released from operating room obligations, the staffing conflict presents a difficult challenge. An agreeable arrangement of service responsibilities must allow the anesthesiologist or his or her delegates to be available to provide safe and consistent care to whomever he or she is responsible, 24 h a day and seven days a week.

Once the intradepartmental resource allocation issues have been discussed with the chairperson, the proposal to begin an acute pain service should be brought to the medical director as a representative of the facility's administrative team. The commitment of the medical director to the project will be necessary to provide resources in the form of personnel and money.

Appropriate leadership for acute pain services must be selected. Operating a service requires a diverse constellation of skills. The service director must have knowledge of the mechanisms of acute post-surgical pain and the methods of treatment, including opioid and non-opioid analgesics, epidural and peripheral nerve catheter placement and maintenance, and ketamine, lidocaine, and other adjuvant drug therapies, as well as treatments for the side effects of these therapies. An anesthesiologist is often the best fit because he or she has experience with these pharmacologic approaches. The recent formation of Accreditation Council for Graduate Medical Studies (ACGME) accredited fellowship programs, combining regional anesthesia and acute pain training, has been in direct response to this understanding that anesthesiology training results in clinicians well suited for providing acute pain management. Indeed, many early acute pain services, like the one started by Dr. Brian Ready at the University of Washington in the 1980s, grew out of the obstetric anesthesia team and the regional anesthetists working thereon. Nonetheless, it is important to distinguish

between a regional anesthetist's goal of keeping a patient comfortable enough to stay *still* for a painful procedure and an acute pain practitioner's goal of keeping a patient comfortable enough to *move* during rehabilitation. Zero out of ten pain is rarely an option or goal for acute pain services. In this regard, as mentioned previously, non-pharmacologic therapies (including physical, psychological, and complementary medicine techniques) also play a role in acute pain treatment, although they are rarely used in the operating room. Acute pain service leaders must be aware of the value and indications for the full panoply of therapeutic strategies for pain.

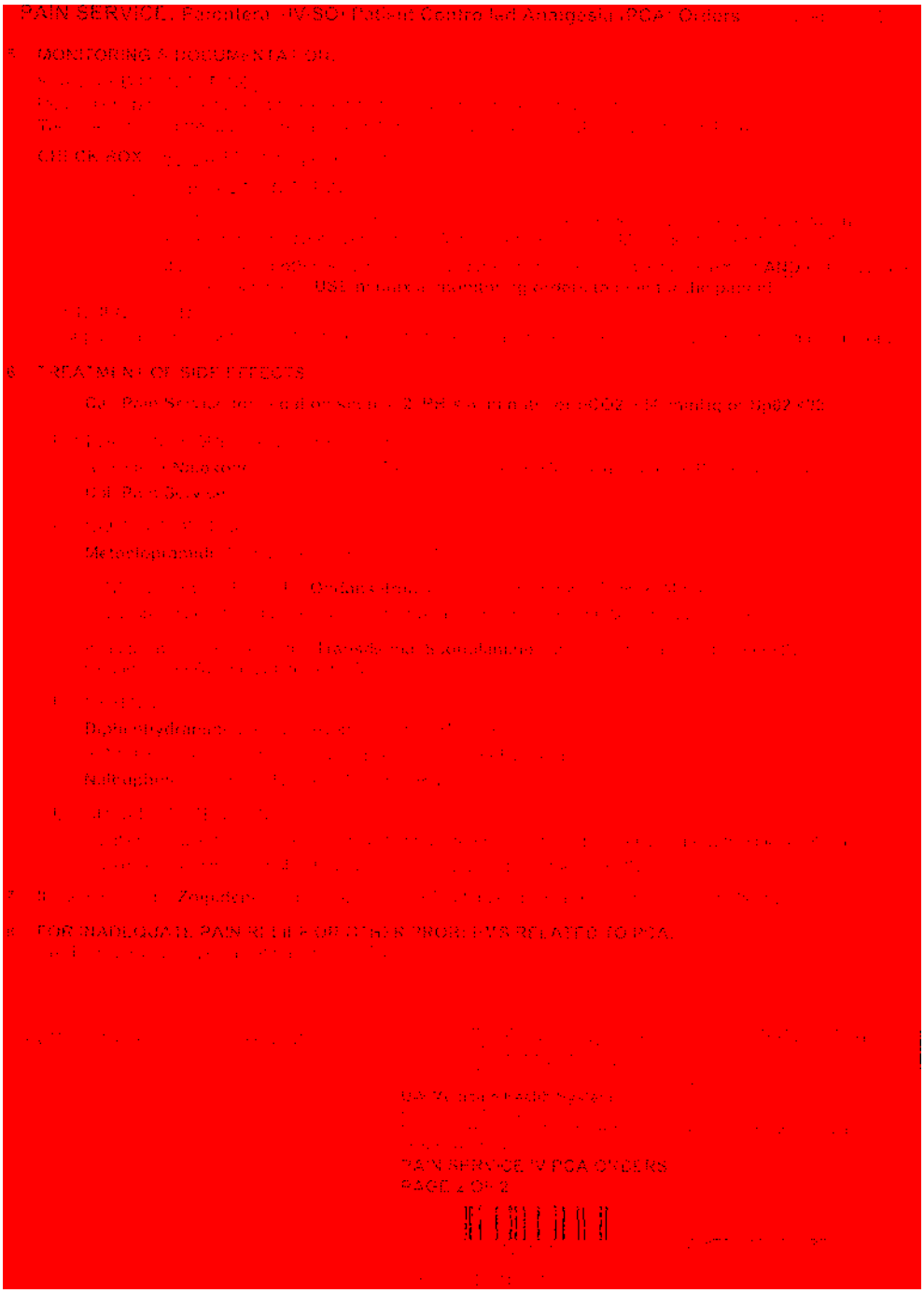
In addition to expertise in analgesic therapies, the success and stability of any new acute pain service will require that the service director also possess certain nonclinical skills, including strong leadership, organizational, communication, and administrative abilities. The clinical success of an inpatient pain service demands the integration of multiple clinical disciplines, such as nursing, anesthesiology, medicine, physical therapy, and pharmacy. The service director must merge the strengths of these diverse professionals such that their efforts are collaborative—both outside of the normal silos inherent to patient care and without undue power struggles or inefficiencies that can arise within a multi-disciplinary team. In addition, the leader will need to understand the place of the acute pain service within the structure of the health care organization. The service should be seen as efficient and valuable to the hospital and its surgical services.



A

• **Figure 3.1** A and B, University of Washington Medical Center parenteral (intravenous/subcutaneous) patient-controlled analgesia standardized order set. Courtesy of University of Washington Medical Center, Seattle, Washington.

B



• **Figure 3.1, cont'd.**

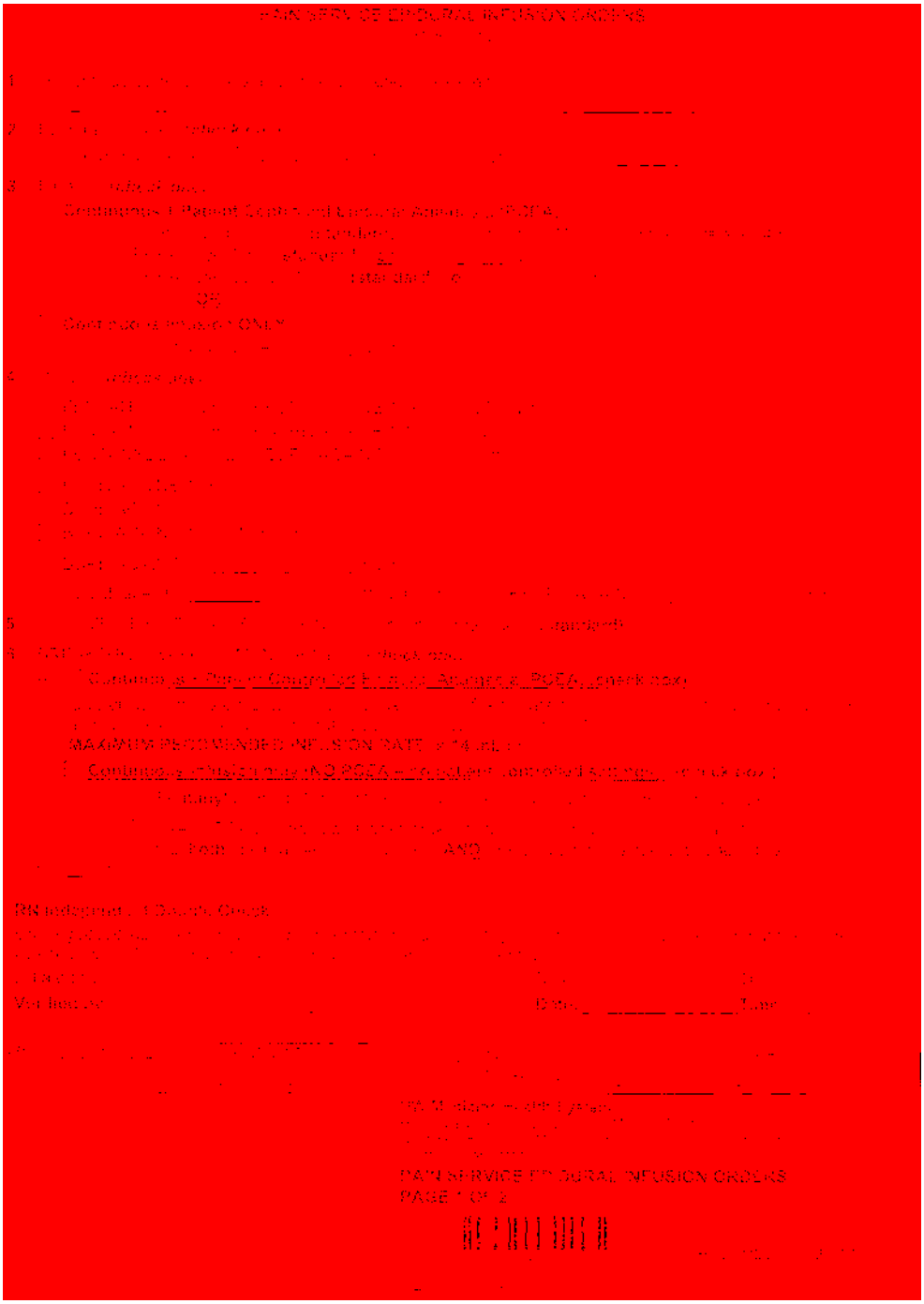
A clinical nurse specialist (CNS) or equivalent is an additional cornerstone on which to build any new inpatient pain service. The primary responsibility of the CNS is to provide ongoing education for intensive care, recovery rooms, and medical/surgical care nurses concerning pain protocols. At the University of Washington Medical Center, a CNS in pain has been a part of the acute pain service from day one (only four different individuals in 35 years). In addition to nursing education, the CNS is involved in equipment trialing and purchasing, order and policy development, committee work on pain-related (though not necessarily pain service-related) hospital committees, and helps to resolve any conflicts that might arise between nursing and prescribing care team members. Over the years, the CNS's salary has been shared to different degrees between departmental and hospital sources.

More recently, pharmacists have begun to play a valuable role in inpatient pain services. Their understanding of drug actions, metabolism, interactions, and side effects has proven ideal for promoting safe pharmacologic pain management. Moreover, their knowledge of drug costs, prescription drug monitoring program benefits and weaknesses, and electronic health record ordering peculiarities have opened the door for practical teaching of

trainees and more experienced practitioners alike. In our inpatient pain service, pharmacists seem to enjoy patient interactions (including symptom assessment and education) and have become vital parts of our multi-professional team.

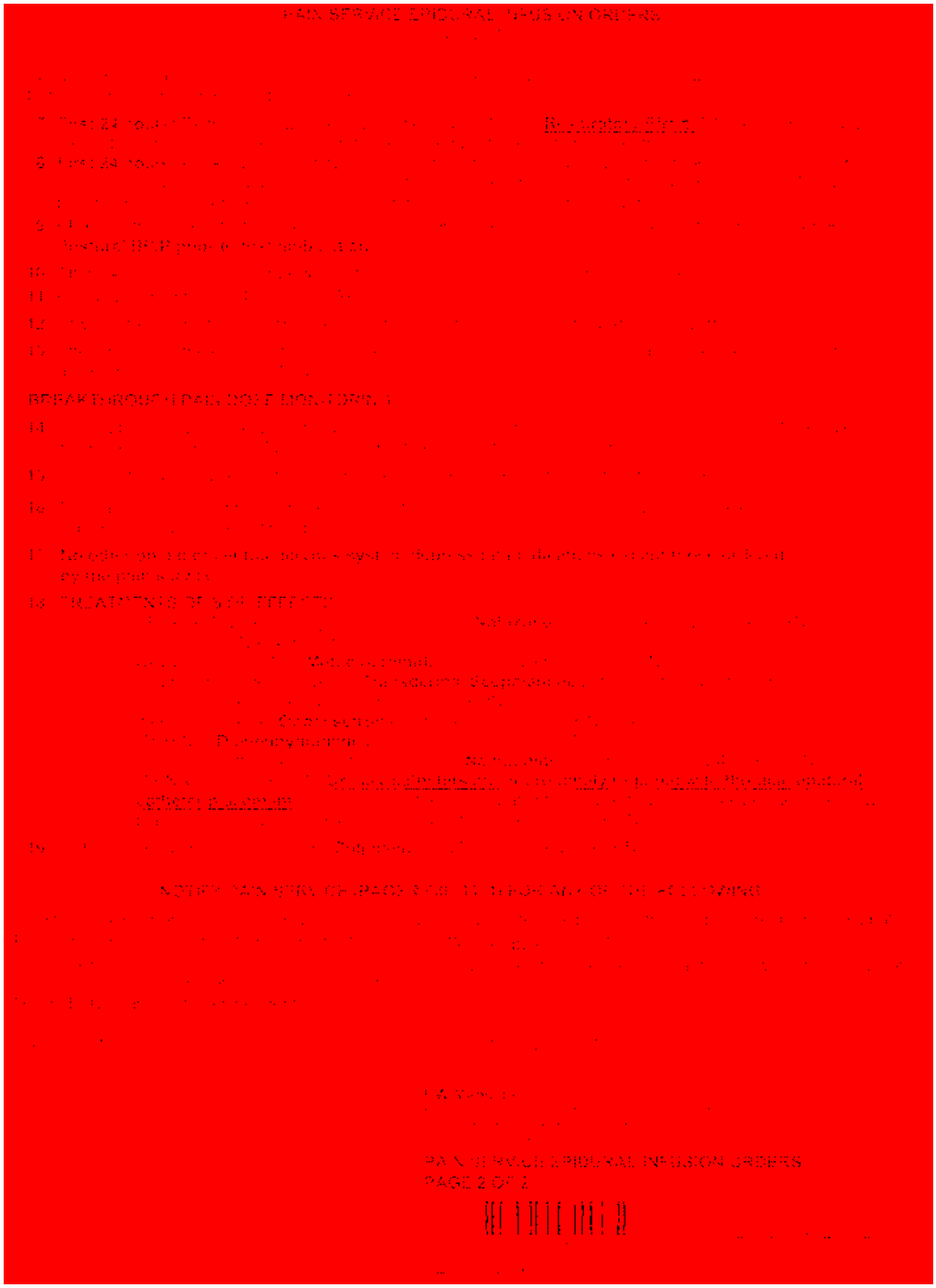
Assessment of Need

Once the challenge of implementing an acute pain service is accepted, and leadership is identified, assessment of specific needs for the service is mandatory. This might be accomplished by surveying the patient population, nurses, types of specialty services, procedures commonly performed, and the people performing these procedures. Furthermore, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has set forth standards declaring the patient's right to adequate pain assessment and treatment and has explicitly acknowledged that pain is a coexisting condition with many diseases and injuries that require explicit attention. Although JCAHO updated its pain-related requirements in 2017,[28] the importance of pain assessment and therapy was not diminished, and the updates were mostly focused on safer opioid prescribing including teaching and practice of multimodal analgesic therapies. This encourages more hospital expertise in



A

• **Figure 3.2** A and B, University of Washington Medical Center epidural infusion standardized order set. Courtesy of University of Washington Medical Center, Seattle, Washington.



B

• **Figure 3.2, cont'd.**

pain management, and on this basis, the mission statement of the service should be defined.

Those planning the structure of the service might also consider whether they wish to distinguish between different types of pain management challenges or manage them as conglomerates. For example, the University of Washington Inpatient Pain Services is divided into three factions: acute pain, chronic/cancer pain, and interventional pain. The service was separated into these groups to preserve the continuity of care (e.g. inpatient admissions of patients followed by an outpatient cancer pain clinic), and more practically manage the high volume of patients (when only a subset of practitioners on a service have the training or experience to perform certain interventional procedures). Admittedly, the boundaries between these categories are artificial and may overlap. For example, consider a patient with acute post-surgical pain superimposed on long-standing cancer pain or a patient who is now recovering from surgery to place an implanted epidural neuromodulating device for treating chronic pain.

Whatever the organizational structure, an acute post-operative pain management service is likely to require 24 h a day and seven

PAIN SERVICE: Pain Management Ketamine Continuous Infusion Orders

1. Prescription:

Drug:	Ketamine – Non Anesthetic Dosing
Concentration:	1mg/mL Send in 250mL normal saline bag
Route:	IV infusion
Infusion Rate: DO NOT TITRATE, DO NOT BOLUS	_____mg/hour (For Postoperative patients: Do not exceed 8mg/hour infusion rate on medical surgical and oncology floors)
Infusion Device:	Standard pain infusion pump Drug is to be secured in locked box with the pump.

2. Change Ketamine bag every 24 hours (related to stability in IVF bag).
   Order next bag in sufficient time to avoid disruption of continuous ketamine infusion.
3. Monitoring and Documentation:
   Ketamine drip initiation: Blood pressure (BP), respiratory rate (RR), pain score, sedation score every 30 minutes for one hour and then every two hours for 8 hours. After 8 hours, monitor RR, pain score, and sedation score every 4 hours while on infusion.
   Ask the patient if they are having hallucinations or unpleasant, disturbing dreams every 8 hours. Document in the clinical record.

   NOTE: Anticipate decreasing opioid requirement/use.

   Infusion rate increases: BP, RR, pain score, sedation score every 30 minutes for one hour, then every two hours for 4 hours and then every 4 hours.

   Check box if special monitoring is required:
   ☐ if patient has **both** neuraxial route (epidural or intrathecal) pain management and Ketamine infusion, **USE neuraxial (epidural or intrathecal) monitoring orders** for RR, pain score and sedation score. BP every 30 minutes for one hour and then every two hours for 8 hours and then every 4 hours.
4. **Call Pain Service pager 986-3334 if**:
   Systolic BP if > or < 30 mm Hg from pre-infusion baseline parameters Baseline BP = _____
   Sedation score > 2 and/or RR < 8 breaths/minute
   Patient reports hallucinations (auditory or visual); feeling dissociated; or reports of unpleasant, disturbing dreams.
   Inadequate pain management
5. Call Pain Service regarding any new orders for opioids or benzodiazepines not ordered by the Pain Service.
6. Patient also has pain service pain management orders for:
   ☐ PCA
   ☐ Neuraxial analgesia (Epidural or Intrathecal)
   ☐ Other: _____

PHYSICIAN/MID LEVEL SIGNATURE	PRINT NAME	PAGER	UPIN/NPI	DATE	TIME

PT.NO

NAME

DOB

UW Medicine
Harborview Medical Center – UW Medical Center
University of Washington Physicians
Seattle, Washington

KETAMINE CONTINUOUS INFUSION ORDERS

U2694

UH2694 REV MAY 09

WHITE - MEDICAL RECORD
CANARY - PHARMACY
PINK - NURSING

PHYSICIAN ORDER – YELLOW

• **Figure 3.3** University of Washington Medical Center intravenous ketamine infusion standardized order set. Courtesy of University of Washington Medical Center, Seattle, Washington.

days a week call coverage, with appropriate medical supervision. Immediate availability is important concerning patient safety and patient satisfaction. Inadequacy of pain relief has been highlighted as a quality-of-care measure and a focus on patients' concerns. In a questionnaire survey, 57% of patients identified pain after surgery as their primary fear.[3] Sadly, the removal of specific questions about pain management satisfaction from the Hospital Consumer Assessment of Healthcare Providers and Systems survey, because of unsubstantiated fears of opioid over-prescribing to improve survey scores, is a step back from incentivizing attention to pain hurdles patients face in recovering from painful conditions or procedures and offers another indication that the multimodal approach to pain management is still not widely appreciated. Nonetheless, the competitive healthcare environment mandates that hospitals focus on the most important issues to patients. Favorable reports of patient satisfaction may encourage patients to seek services in a given hospital facility and encourage patient loyalty in return for additional medical care. Furthermore, according to one multicenter prospective cohort study,[29] immediate post-operative patient satisfaction with care is a predictor of long-term, positively self-perceived health status. In short, for many hospitals, following JCAHO's requirement to have a "leadership team that is responsible for pain management" is also simply put, the right thing to do for their patients.

PAIN SERVICE: Pain Management IV Lidocaine Continuous Infusion Orders

Admit / Tx / Medication

GENERAL GUIDELINES:1. No Titration or bolus. 2. No routine therapeutic drug level monitoring. 3. Generally used for 24-72 hours as an adjunct to existing pain treatments (including epidural, PCA and ketamine for analgesia). 4. Select dose below according to patient weight (MAXIMUM rate = 120 mg/hr

Patient weight < 45 kg = Lidocaine 30 mg/hr IV infusion
Lidocaine 2g in D5W (Dextrose 5% in Water) 250mL
Comments: For PAIN. DO NOT titrate, DO NOT bolus

Patient weight 45-55 kg = Lidocaine 75 mg/hr IV infusion
Lidocaine 2g in D5W (Dextrose 5% in Water) 250mL
Comments: For PAIN. DO NOT titrate, DO NOT bolus

Patient weight 56-67 kg = Lidocaine 85 mg/hr IV infusion
Lidocaine 2g in D5W (Dextrose 5% in Water) 250mL
Comments: For PAIN. DO NOT titrate, DO NOT bolus

Patient weight 68-80 kg = Lidocaine 100 mg/hr IV infusion
Lidocaine 2g in D5W (Dextrose 5% in Water) 250mL
Comments: For PAIN. DO NOT titrate, DO NOT bolus

Patient weight > 80 kg = Lidocaine 120 mg/hr IV infusion
Lidocaine 2g in D5W (Dextrose 5% in Water) 250mL
Comments: For PAIN. DO NOT titrate, DO NOT bolus

Vitals / Monitoring

Vital Signs
Lidocaine initiation: BP, HR, respiratory effort (rate, depth, regularity & effort), 02 sat, visual analogue scale (VAS) pain score q1h × 2, then q2h × 2, then q4h if stable

Cardiac Monitoring
It is the responsibility of the ordering provider to assure that a 12 lead EKG has been obtained within the previous 7 days and showed no contraindications (including 1st and 2nd degree heart block)

Neuro Checks
Neuro checks and monitoring for adverse effects/toxicity signs including: disorientation,or confusion, slurred speech, dizziness, sedation, seizure q1h × 2, then q2h × 2, then q4h if stable

Pt Care / Nursing

Call Provider for the Following Vital Signs
SBP> 160, SBP< 90, DBP< 50, RR< 8, and/or sedation scale > 2, if systolic BP is > or < 30 mm Hg from pre-infusion baseline parameters. New development of arrhythmia. CALL or page the Acute PAIN SERVICE (APS) and Primary Service

Call Pain Service for the following signs or symptoms (see order comments) and STOP infusion immediately.
Comments: Patient Assessments: 1) seizure 2) tremor 3) diplopia 4) metallic taste 5) numbness of tongue 6) tinnitus 7) muscle twitching. Provider should consider drawing lidocaine level STAT if side effects are severe. (Please note: this has no therapeutic consequence and is to rule out other etiologies)

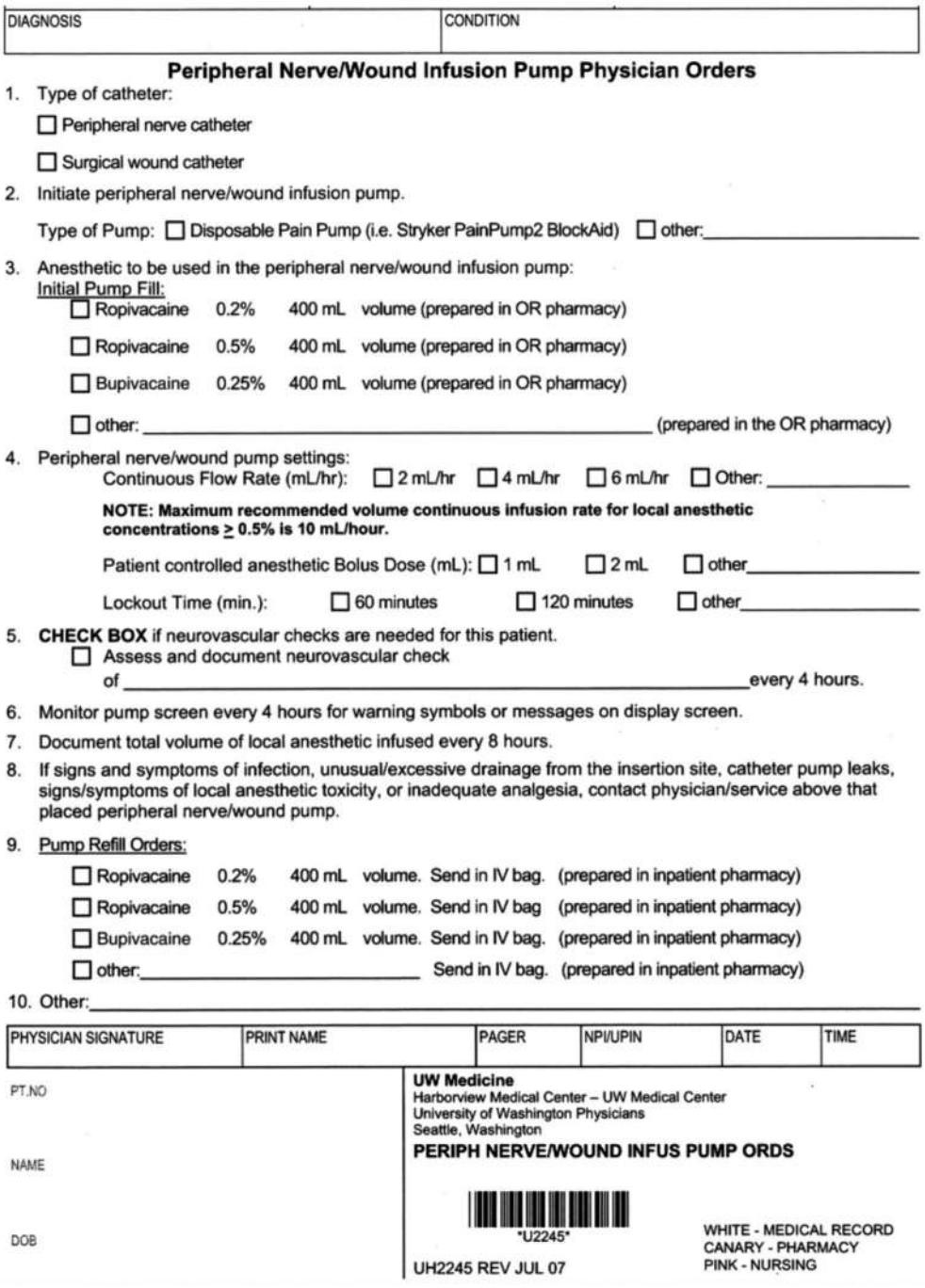
In the very rare event of Local Anesthetic-induced Systemic Toxicity (LAST) call a CODE BLUE immediately and implement: 1. Airway management to deliver Oxygen, 2. Seizure suppression with benzodiazepines, 3. Cardiopulmonary stabilization/resuscitation

• **Figure 3.4** University of Washington Medical Center intravenous Lidocaine infusion standardized order set. Courtesy of University of Washington Medical Center, Seattle, Washington.

Definition of the Service

Once the pain service mission statement has been formulated in response to the perceived institutional and community needs, leadership must define the resources that will be required to meet the needs. The resources and modalities that an acute pain service may use are diverse and depend on the patient population, the skills of the personnel, and the service's therapeutic approach. Ideally, an evidence based approach to the selection of treatment modalities that specifically evaluates the efficacy and cost-effectiveness of each therapy is used. The resources required to implement and operate an acute pain service will represent a synthesis of characteristics of the patient population, evidence based selection of therapeutic modalities, and consistency with the service's mission.

The feasibility of various treatment plans based on the availability of resources was defined by the IASP task force for the management



DIAGNOSIS	CONDITION

Peripheral Nerve/Wound Infusion Pump Physician Orders

1. Type of catheter:
   - ☐ Peripheral nerve catheter
   - ☐ Surgical wound catheter
2. Initiate peripheral nerve/wound infusion pump.
   Type of Pump: ☐ Disposable Pain Pump (i.e. Stryker PainPump2 BlockAid) ☐ other:_____
3. Anesthetic to be used in the peripheral nerve/wound infusion pump:
   Initial Pump Fill:
   - ☐ Ropivacaine 0.2% 400 mL volume (prepared in OR pharmacy)
   - ☐ Ropivacaine 0.5% 400 mL volume (prepared in OR pharmacy)
   - ☐ Bupivacaine 0.25% 400 mL volume (prepared in OR pharmacy)
   - ☐ other: _____ (prepared in the OR pharmacy)
4. Peripheral nerve/wound pump settings:
   Continuous Flow Rate (mL/hr): ☐ 2 mL/hr ☐ 4 mL/hr ☐ 6 mL/hr ☐ Other: _____
   NOTE: Maximum recommended volume continuous infusion rate for local anesthetic concentrations ≥ 0.5% is 10 mL/hour.
   Patient controlled anesthetic Bolus Dose (mL): ☐ 1 mL ☐ 2 mL ☐ other_____
   Lockout Time (min.): ☐ 60 minutes ☐ 120 minutes ☐ other_____
5. **CHECK BOX** if neurovascular checks are needed for this patient.
   ☐ Assess and document neurovascular check
   of _____every 4 hours.
6. Monitor pump screen every 4 hours for warning symbols or messages on display screen.
7. Document total volume of local anesthetic infused every 8 hours.
8. If signs and symptoms of infection, unusual/excessive drainage from the insertion site, catheter pump leaks, signs/symptoms of local anesthetic toxicity, or inadequate analgesia, contact physician/service above that placed peripheral nerve/wound pump.
9. Pump Refill Orders:
   - ☐ Ropivacaine 0.2% 400 mL volume. Send in IV bag. (prepared in inpatient pharmacy)
   - ☐ Ropivacaine 0.5% 400 mL volume. Send in IV bag (prepared in inpatient pharmacy)
   - ☐ Bupivacaine 0.25% 400 mL volume. Send in IV bag. (prepared in inpatient pharmacy)
   - ☐ other:_____ Send in IV bag. (prepared in inpatient pharmacy)
10. Other:_____

PHYSICIAN SIGNATURE	PRINT NAME	PAGER	NPI/UPIN	DATE	TIME

PT.NO

NAME

DOB

UW Medicine
Harborview Medical Center – UW Medical Center
University of Washington Physicians
Seattle, Washington

PERIPH NERVE/WOUND INFUS PUMP ORDS

U2245

UH2245 REV JUL 07

WHITE - MEDICAL RECORD
CANARY - PHARMACY
PINK - NURSING

• **Figure 3.5** University of Washington Medical Center peripheral nerve/wound infusion standardized order set. Courtesy of University of Washington Medical Center, Seattle, Washington.

of acute pain (Table 3.1). Individualized treatment of patients should ideally be evidence based (Table 3.2), and several organizations have published guidelines for acute pain treatment.[30,31] A useful, more dynamic resource for evidence based post-operative pain management is the PROSPECT database[32]—hosted and updated by the European Society of Regional Anesthesia and Pain Therapy. This website (https://esraeurope.org/prospect/) offers procedure specific post-operative pain management (PROSPECT) recommendations based on evidence detailed on the site. Such recommended care mixes maximal improvements in patient outcomes with the most cost-effective care available. Indeed, many of the leaders of the PROSPECT project have also spearheaded the so called ERAS (Enhanced Recovery After Surgery) movement to facilitate safe and efficient post-surgical rehabilitation, minimizing hospital stays and thus reducing costs.[33] For example, Dr. Henri Kehlet (a general surgeon) has developed ERAS principles for more than 35 years—emphasizing rapid re-feeding after bowel surgery, including, in part, the use of neuraxial local anesthetics for post-operative pain. Such techniques require special resources in the form of medications, equipment, and personnel, and these must be anticipated and negotiated with the institution's administrative, business, and clinical departments when designing the service structure.

TABLE 3.1 **Options for Acute Pain Treatment Based on Available Resources**

TABLE 3.1A **Attention! When can you Safely do Neuraxial/Peripheral Nerve Procedures or Give Antithrombotic Agents?**
NOTE: For Concerns Related to Bleeding or Traumatic Procedures, Contact Pain Service.

Precautions:

Do NOT give MULTIPLE anticoagulants, including antiplatelet agents, concurrently in patients undergoing Neuraxial/Nerve Procedures.
Delay restarting anticoagulants for 24 h after traumatic needle placement.

MEDICATION	PRIOR TO NEURAXIAL/NERVE PROCEDURE Minimum time between the last dose of antithrombotic agent AND neuraxial injection or neuraxial/nerve catheter placement	B. WHILE NEURAXIAL/NERVE CATHETER IN PLACE Restrictions on the use of antithrombotic agents while neuraxial/nerve catheters are in place and prior to their removal	AFTER NEURAXIAL/NERVE PROCEDURE Minimum time between neuraxial injection or neuraxial/nerve catheter removal AND next dose of antithrombotic agent
ANTICOAGULANTS FOR VTE PROPHYLAXIS			
Heparin unfractionated 5000 units SQ Q8H or Q12H	Maybe give; no time restriction for neuraxial injection or neuraxial/nerve catheter placement **Does not require Pain Service approval**		
* **Heparin** unfractionated 7500 units SQ Q8H	12 h	**CONTRAINDICATED while catheter in place. May NOT be given unless approved by Pain Service or Obstetric Anesthesia Attending**	4 h
* **Dalteparin** (Fragmin) 5000 units SQ QDay * **Enoxaparin** (Lovenox) 40 mg SQ QDay	12 h - CrCl ≥30 mL/min 24 h - CrCl <30 mL/min	**May be given BUT:** • **Must wait for 8 h after catheter PLACEMENT before giving the dose** • **Must wait for 12 h after the last dose before REMOVING catheter**	4 h
* **Enoxaparin** (Lovenox) 30 mg SQ Q12H or 40 mg SQ Q12H	12 h - CrCl ≥30 mL/min 24 h - CrCl <30 mL/min	**CONTRAINDICATED while catheter in place. May NOT be given unless approved by Pain Service or Obstetric Anesthesia Attending**	4 h
Fondaparinux (Arixtra) 2.5 mg SQ QDay	48 h - CrCl ≥30 mL/min CrCl <30mL/min: Call Hematology		6 h
Apixaban (Eliquis) 2.5 mg bid	48 h - CrCl ≥50 mL/min 72 h - CrCl ≥30–50 mL/min CrCl <30 mL/min: Call Hematology	**May be given BUT:** • **Must wait for 8 h after catheter PLACEMENT before giving the dose** • **Must wait for 12 h after the last dose before REMOVING catheter**	6 h
Rivaroxaban (Xarelto) 10 mg po QDay	48 h - CrCl ≥50 mL/min 72 h - CrCl ≥30–50 mL/min CrCl <30 mL/min: Call Hematology		
Betrixaban (Bevyxxa) 80 mg QDay	72 h - CrCl ≥30 mL/min 96 h - CrCl ≥15–30 mL/min CrCl <15 mL/min: Call Hematology		

IM, Intramuscular; *IV*, intravenous; *vPCA*, patient-controlled analgesia; *PO*, by mouth; *PPV*, positive pressure ventilation; *PR*, by rectum; *SQ*, subcutaneous; *TENS*, transcutaneous electrical.

TABLE 3.1B Agents Used for Full Systemic Anticoagulation

Apixaban (Eliquis) 2.5 mg bid - 10 mg bid	48 h - CrCl ≥50 mL/min 72 h - CrCl 30–50 mL/min CrCl <30 mL/min: Call Hematology	**CONTRAINDICATED** **While catheter in place.** **May NOT be given unless approved by Pain Service or Obstetric Anesthesia Attending**	6 h
Rivaroxaban (Xarelto) 15–20 mg po QDay or 15 mg bid	48 h - CrCl >50 mL/min CrCl <50 mL/min: Call Hematology		
Edoxaban (Savaysa) 30–60 mg QDay	48 h - CrCl ≥50 mL/min CrCl <50 mL/min: Call Hematology		
Dabigatran (Pradaxa) 75 mg bid - 150 mg bid	72 h - CrCl 50 mL/min 120 h - CrCl 30–50 mL/min CrCl <30 mL/min: Call Hematology		
Fondaparinux (Arixtra) 5–10 mg SQ QDay	72 h - CrCl ≥30 mL/min CrCl <30 mL/min: Call Hematology		
Dalteparin (Fragmin) 200 Units/kg SQ QDay or 100 Units/kg SQ Q12H	24 h - CrCl ≥30 mL/min 48 h - CrCl <30 mL/min		4 h
Enoxaparin (Lovenox) 1.1–1.5 mg/kg SQ QDay or 1 mg/kg SQ Q12H	24 h - CrCl ≥30 mL/min 48 h - CrCl <30 mL/min		
Heparin unfractionated IV infusion	when aPTT normal or anti-Xa activity is undetectable		
Heparin unfractionated full dose SQ	when aPTT normal or anti-Xa activity is undetectable		
Warfarin (Coumadin)	when INR ≤1.5		
DIRECT THROMBIN INHIBITORS, INJECTABLE			
Argatroban IV continuous infusion	when DTI assay <40 or aPTT <40 s	CONTRAINDICATED While catheter in place. May NOT be given unless approved by Pain Service or Obstetric Anesthesia Attending	4 h
Bivalirudin (Angiomax) IV continuous infusion	when DTI assay <40 or aPTT <40 s		

TABLE 3.1C Antiplatelet Agents Pages 285–286

Aspirin or NSAIDs	**May be Given; No Time Restrictions for Neuraxial Injection or Neuraxial/Nerve Catheter Placement Does Not Require Pain Service Approval**		
Abciximab (Reopro) IV continuous infusion	48 h	CONTRAINDICATED while catheter in place. May NOT be given unless approved by Pain Service Attending	6 h
Aspirin/ dipyridamole (Aggrenox)	24 h		
Cangrelor (Kengreal) IV continuous infusion	3 h		
Clopidogrel (Plavix)	Seven days		
Prasugrel (Effient)			
Ticagrelor (Brilinta)			
Tirofiban (Aggrastat) IV continuous infusion	8 h-CrCL > 50 mL/min CrCl < 50 Call Hematology		
Eptifibatide (Integrelin) IV continuous infusion			

TABLE 3.1C Antiplatelet Agents Pages 285–286—cont'd

Aspirin or NSAIDs	**May be Given; No Time Restrictions for Neuraxial Injection or Neuraxial/Nerve Catheter Placement Does Not Require Pain Service Approval**		
	THROMBOLYTIC AGENTS		
Alteplase (TPA) 1 mg dose for catheter clearance	May be given; no time restriction for neuraxial injection or neuraxial/nerve catheter placement Does not require Pain Service approval (Maximum dose 4 mg/24 h)		
Alteplase (TPA) full dose for stroke, MI	48 h	CONTRAINDICATED while catheter in place. Mat NOT be given unless approved by Pain Service Attending	Ten days

Horlocker TT, Vandermeulen E, Kopp SL, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence Based Guidelines (fourth edition). *Reg Anesth Pain Med.* 2018;43(3):263–309.

Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis.* 2016;41(1):206–232.

TABLE 3.2 Evidence Based Guides for the Treatment of Acute Pain

Analgesic Technique	Personnel*	Knowledge	Skills†	Equipment‡	Comment§
Basic anxiety eduction	Any				1,8, 9
PO/PR nonopioids	A, B	Dose, range, side effects	M, N		1, 8, 9
PO/PR opioids	A, B	Dose, range, side effects	M,N		1, 8, 9
SC/IM opioids	A, B, G	Dose, range, side effects	M, N, O, R	T	1, 8, 9
IV opioids	A, B, G	Dose, range, side effects, loading titration	M, N, O, P, R	T, U, W, X, Y	1, 8, 9
Local anesthetic infiltration	B	Anatomy, dose, range, side effects	M, R, S, T		4, 7
Opioid PCA	A, C or E, G	Dose, range, side effects, PCA principles	M, N, P	U, V, X,Y	8, 9
Ketamine	c	Dose, range, side effects	M, N, P, R	U, W, X, Y	4
Nitrous oxide	B	Dose, range, side effects, administration	M, N, R	Delivery system	4, 8
TENS	A, B	Anatomy	M	Units, accessories	Adjunctive therapy
Intraspinal opioids	A, C, E	Dose, range, side effects	M, N, P, Q, R	T, U, W, X, Z	1, 2, 8, 9
Plexus blocks	A,C	Dose, range, side effects, anatomy	M, N, P, Q, R, S	T, W, X, Y	2
Neuraxial block	A,C	Dose, range, side effects, anatomy	M, N, P, Q, R, S	T, U, W, X, Y, Z	1, 2, 3, 5, 6, 7, 8
Interpleural	A,C,D,E	Dose, range, side effects, anatomy	M, N, P, Q, R, S	T, U, W, X, Y, Z	1, 3, 7
Cryoanalgesia	E, D	Anatomy		Delivery system	1, 3, 7
Psychological support	A, B,C, D, E, F	Coping strategies	Relaxation, breathing exercises	All the above	Time-consuming, adjunct
Acute pain service	A, C, D, E, F, G	All of the above	M, N, O, P, Q, R, S, leadership		Policies, procedures, education, quality assurance

After the resources are defined, the range of therapeutic services to be offered can be determined. The principles of post-operative pain therapy that must be implemented in each patient interaction on the service include:

1. Evaluation of the source and severity of the pain.
2. Understanding the relationship between pain and other components of suffering (e.g. poor prognosis creating reactive depression or anxiety).
3. Achieving and maintaining adequate pain relief and incorporating it into the acute rehabilitation scheme.
4. Refining therapies based on individual needs.

These goals can be achieved through pain services built on different therapeutic emphases. For example, a *single-modality service* allows the provision of analgesia with intravenous opioid systems to all inpatients and the provision of regional analgesia in select instances. This model can be nurse-based with physician supervision and offers a safe, limited, and cost-effective method for the treatment of post-operative patients. On the other hand, a multimodal service includes diverse healthcare professionals from a variety of domains. Extracting and integrating the relevant expertise from these professionals on such services is critical for individualized and optimized pain management. Professionals commonly utilized include psychologists, pharmacists, physical and occupational therapists, nutritionists, and spiritual care providers, in addition to physicians and nurses. The comprehensive approach of multi-disciplinary pain service functions is ideal for inpatients with the most complicated pain issues. Examples include patients with chronic pain suffering from acute exacerbations and post-surgical patients with severe opiate tolerance following long-term opioid treatment. This multi-professional model has been most frequently used in the context of inpatient palliative care consultation at the end of life, but this approach, or some mild modification of it, has utility in the acute care arena as well.[34]

Ongoing quality assurance can be managed on a service, departmental, and/or institutional level but should be transparent to participants and provide an opportunity for feedback and improvement for team members (including trainees and faculty) and service policies and procedures. We have used multi-professional team meetings—no less frequently than every two months as forums to communicate new or updated policies or procedures, clinical questions or concerns, cases of morbidity or mortality, and upcoming or ongoing research updates.

Financing and the Business Plan

The next step in the process of organizing an inpatient acute pain service is to construct a business plan. This is often the most challenging phase because the financial and business skills needed may not be innate to clinical anesthesiologists and are rarely covered in their training. The value analysis of this type of service is not entirely monetary. It should be emphasized that although the cost of delivering care may be considerable, the calculation of the cost analysis is a more complicated determination. The ideal measurement of the utility for pain management is controversial. Researchers have examined outcome measures, including hospital stay, hospital readmissions, quality of life, and clinical productivity.[35] However, regardless of the cost analysis, there is a cultural expectation and ethical imperative supporting the philosophy that appropriate treatment of pain is independently valuable. The JCAHO has emphasized this sentiment in their statement that appropriate pain management is "good medicine" and that pain assessment and pain management should be "an organizational priority."[28,36] With that acknowledgment, the purpose of an acute pain service business plan is to describe the inner workings of the proposed service, including its organizational strategy, marketing plan, tentative schedule for implementation, and overall cost. This must occur before the first cent is spent on the project. The business plan has two primary components.

The first arm of the plan is a narrative that includes the mission statement, its structure, and the responsibilities of the service. Here, the job descriptions of the involved personnel are outlined, facility requirements are listed, and the marketing plan is presented. This document should clarify the role, responsibilities, duties, and expectations of various personnel that are key to a successfully operating service. Guidelines and manuals for nurses and house staff are key to this first portion of the business plan.

The second primary component of the business plan is prepared as a spreadsheet that outlines the finances of the business endeavor, and these estimates must be as accurate as possible. Estimates of fixed and variable incomes, startup capital necessary until revenue produces profit, and a month by month expenditure estimate for at least the first year must be among the data provided in this document.

The plan should also consider the acquisition costs of analgesic medications and other pharmacy costs. Macario and McCoy reviewed the records of 298 patients who underwent hip or knee replacement surgery and found that pharmacy costs accounted for only 3% of the total hospital cost. However, the costs of post-operative analgesics represented 31% of the total pharmacy cost.[37] Intravenous acetaminophen is an example of a useful addition to our analgesic armamentarium, but its absolute indications are few. Studies have demonstrated that intravenous and oral acetaminophen are equally effective for pain,[38] despite their hundred-fold difference in cost. In our hospital, intravenous acetaminophen is to be administered only after acute pain team discussion, and indications for use include only functionally significant pain, patients who can have nothing by mouth including medications, and a contraindication or insufficiency of nonsteroidal anti-inflammatory drugs. If intravenous acetaminophen is approved by the pain team (including the pain service pharmacist), it is only approved for 24 h, at which time indications are assessed again. Similarly, in the last few years, millions of doses of liposomal bupivacaine have been infiltrated by surgeons and anesthesiologists (at hundreds of dollars per dose). However, third-party payers have had very restricted reimbursement policies for the drug, and initial meta-analyses demonstrated limited evidence of clinical advantages over plain bupivacaine (at 1/100th its cost).[39,40] Liposomal local anesthetics may well be found to be efficacious and cost effective in their pain-relieving effects for certain inpatient and/or outpatient procedures or patients. However, it is unlikely that anyone is better positioned to help hospital administrators balance hospital cost and evidence based analgesic efficacy in such therapeutic decision making than acute pain service leadership.

Other cost drivers include human resources in the form of pharmacists and nurses, as well as equipment, including PCA and epidural pumps. Medication errors are another rarely considered factor that increases the cost of post-operative analgesia. Adverse drug events, for example, have been shown to result in extending hospital stay by 4.6 days at a cost of $5857 per patient.[41]

Finally, in this section of the business plan, it is ideal to have an estimate of the anticipated monthly patient load and the minimum number of patients required to support service expenses. This is not as easy a calculation as it might seem and needs to include a discussion of anticipated challenges to reimbursement

either within or outside the institution. For instance, it is necessary to examine the insurance characteristics of the patient population that the acute pain program will serve. Based on the payer mix or the percentage of the population that is served by health maintenance (HMO), preferred provider (PPO), and medical care (MCO) organizations, it may be necessary to arrange plans for the preauthorization of acute pain services with the administrators of local health plans. Additionally, there may be geographical region-specific rules for billing pain services. Post-operative pain services are bundled under Medicare surgical services fees. In our Medicare region, we must provide evidence of a request from the attending surgeon for help with pain management and why such services are requested. For this reason, we have created a pain service consult "order" with several common reasons for pain consultation listed (e.g. opioid tolerance, and regional analgesia evaluation) and have provided this electronic list both as a freestanding order and embedded in the pre-operative surgical order set. We ask our surgical colleagues to fill out this request for service but have thus far chosen not to withhold pain treatment from patients with extreme pain when awaiting electronic referral.

In the construction of the business plan, the total revenue minus the total cost will produce a *predicted* financial position. This calculation begins with the estimation of the approximate charge per patient for each therapeutic modality to be used. With this revenue in mind, the cost of providing the service and various therapeutic modalities can be determined. Ideally, the financial design of the acute pain service should include elements promoting flexibility as the patient loads waxes and wanes. This is best accomplished by shifting fixed costs (e.g. permanent employees) to variable costs (e.g. temporary employees) as much as possible. Note that the result of this calculation will fluctuate over time. The financial solvency of the service will be most protected by hoping for the best while planning for the worst-case scenario.

Billing and Collection

A well-organized structure for billing and collecting services is imperative to ensure the solvency of any medical organization. Knowledgeable personnel, the necessary hardware, and efficient software for data collection are necessary if the service's business plan includes an internal billing and collection group. As medical coding and billing accelerate in complexity and specificity, many organizations have elected to employ outside billing and collection services that operate on percentage-based contracts.

It is crucial to be aware of the current Centers for Medicare and Medicaid Services (CMS) guidelines for documentation and billing and to remain informed about modifications as they occur. Accurate documentation of services will facilitate correct and timely reimbursement, as well as represent what was actually done in the medical record. Furthermore, accurate documentation will clarify what was not done for the reference of both other healthcare professionals and third-party payers, thereby avoiding time-consuming changes in documentation, fines, and even criminal charges if discrepancies between CMS guidelines and physician billing are judged to be fraudulent. Example reference guides regarding chart notation and current CMS-required documentation can be found in the Appendices F. At our particular teaching institution, we have found it useful to "bake" some of the billing criteria into the electronic medical record pain consult note and progress note templates with the use of "hard stops" for vital assessment fields. Documentation of appropriate pain assessments, including analgesic-related side effects, often ensures that suitable levels of billing are accomplished.

Over the last several years at the University of Washington Medical Center, we have transitioned from a resident home night call model to using a team of trained nurse practitioners and physician assistants working in the hospital at night with pain attending home availability for questions (as before). This arrangement has improved patient and nursing satisfaction with a member of the pain team in house and available 24/7 despite only a minimal increase in net personnel costs because we can now bill for post-operative day zero pain assessment and treatment. This additional billing is appropriate, and perhaps even overdue, as, often, the most important pain assessments and treatments occur in the first few hours after surgery,[29] when the pain team might have previously been at home.

Marketing Plan

Once the design and planning of the new acute pain service have been completed, a marketing plan will be important to promote its utilization. Potential referring providers and patients will need to be introduced to the concept and the benefits that the service offers. Although conventional medical education often leaves physicians naive to the business and marketing dimensions of medicine as an industry, help can be garnered from the hospital's public relations office or a private marketing firm. Implementation of the marketing plan is another cost that must be considered in the service budget. Marketing strategies must be designed carefully. It should present a consistent image of the mission and services offered by the budding acute pain service in light that emphasizes the added value to patient care. The marketing strategy may also delicately make a case for the potential cost and convenience of using the new service. Methods for circulating such information may include announcements and brochures, professionally prepared stationary, logos, newsletters, and websites.

Internal education is another vital part of the marketing of acute pain services. Frequent positive interactions between the acute pain service and other departments and their personnel (e.g. presentations at interdepartmental case conferences) are crucial for increasing the visibility of the service and expanding its referral base. In an academic institution, this might also include the involvement of non-anesthesiology residents in the service. When residents rotating from other specialties participate, particularly from the surgical department, they can learn about the treatment modalities offered and the advantages that they provide. Furthermore, several years ago, when we began having anesthesiology residents rotate on the pain service for a month during their pre-anesthesia intern year, we were surprised at the interns' adeptness and seeming enjoyment of the service but also by how we benefited from having "under-cover pain experts" on teams throughout the hospital during the interns' other 11 months. In addition, the importance of education and involvement of nursing and pharmacy colleagues (and their students) cannot be overestimated in helping to grow a pain service since these colleagues are often in a position to suggest that a patient be referred to the acute pain service.

Finally, the marketing plan of an acute pain service should align itself with the JCAHO and its standards and expectations previously described.[28] Implementation and compliance with these standards should serve to propel an acute pain service toward success, given that both aim to make safe pain management a top priority.

Future Service Flexibility

Even after the implementation of an acute pain service, leaders of the service must remain attentive and responsive to changes in the pain care needs of patients, colleagues, or the institution. For instance, recent advances in disposable pump technology have allowed us to offer peripheral nerve blocks on an outpatient basis as surgeries have shifted increasingly to an outpatient setting. Our inpatient acute pain nocturnist team is available at night by telephone should there be any questions or concerns from these patients. On the other hand, our daytime regional anesthesia team educates these patients before discharge (including a written instructional document) and routinely contacts them by phone on post-operative day one to inquire about patient questions and level of satisfaction with their pain care. Whether future advancements in treatments or technology will allow us to provide further evolution of services provided by our inpatient pain team remains to be determined. However, public health and individual complexities in pain management have already prompted us (and others) to use expertise gained from the inpatient pain service to influence safe pain management practices throughout the healthcare system.

Perioperative Pain Clinic

Some inpatient acute pain services have recently been used to provide additional outpatient perioperative pain clinic services as a way of educating, planning, and helping our surgical colleagues manage the most complex post-operative pain patients. Although rules and guidelines by various national societies, legislatures, and insurance carriers have been incorporated into institutional protocols for the management of post-operative pain (sometimes based on actual evidence [30,32.42,43]), there is a subset of patients for whom the standard plan of care is still inadequate. Patients with a history of chronic pain or addiction, who have a history of pain that is difficult to control, or who are at risk for developing chronic post-surgical pain might require a more involved multi-tiered approach to pain in the surgical setting.[44] The development of a perioperative pain management service is one way to improve care for such patients.

Perioperative pain management seeks to bridge the pre-operative, intraoperative, and post-operative periods through patient education and expectation management, enhanced interdisciplinary communication, and expert specialist care throughout the perioperative period. The general principles for treating post-operative pain apply to the rationale for such a service:

- First, as previously mentioned, surveyed patients rate pain control, especially immediately after surgery, as one of their highest concerns and priorities.[45]
- Second, safe and adequate pain control has been shown to reduce post-operative opioid consumption, decrease inpatient hospital length of stay, and prevent the development of chronic pain after surgery.[46]
- A perioperative pain service (in contrast to a more limited inpatient pain service) can give a more structured methodology for treating acute post-operative pain in a specific "at risk" group of patients.[47]
- Finally, a perioperative pain clinic provides another layer of care and safety for the patient, their outpatient providers, and surgeons in the management of perioperative opioid consumption.

In fact, at this time, there are currently few perioperative pain clinics or services nationwide.[49] Therefore the ideal model for such services has yet to be established, and such clinics' long-term effectiveness awaits further study. However, reports from perioperative clinics that are currently operating suggest an improvement in patient outcomes with this intervention and share several characteristics.[48]

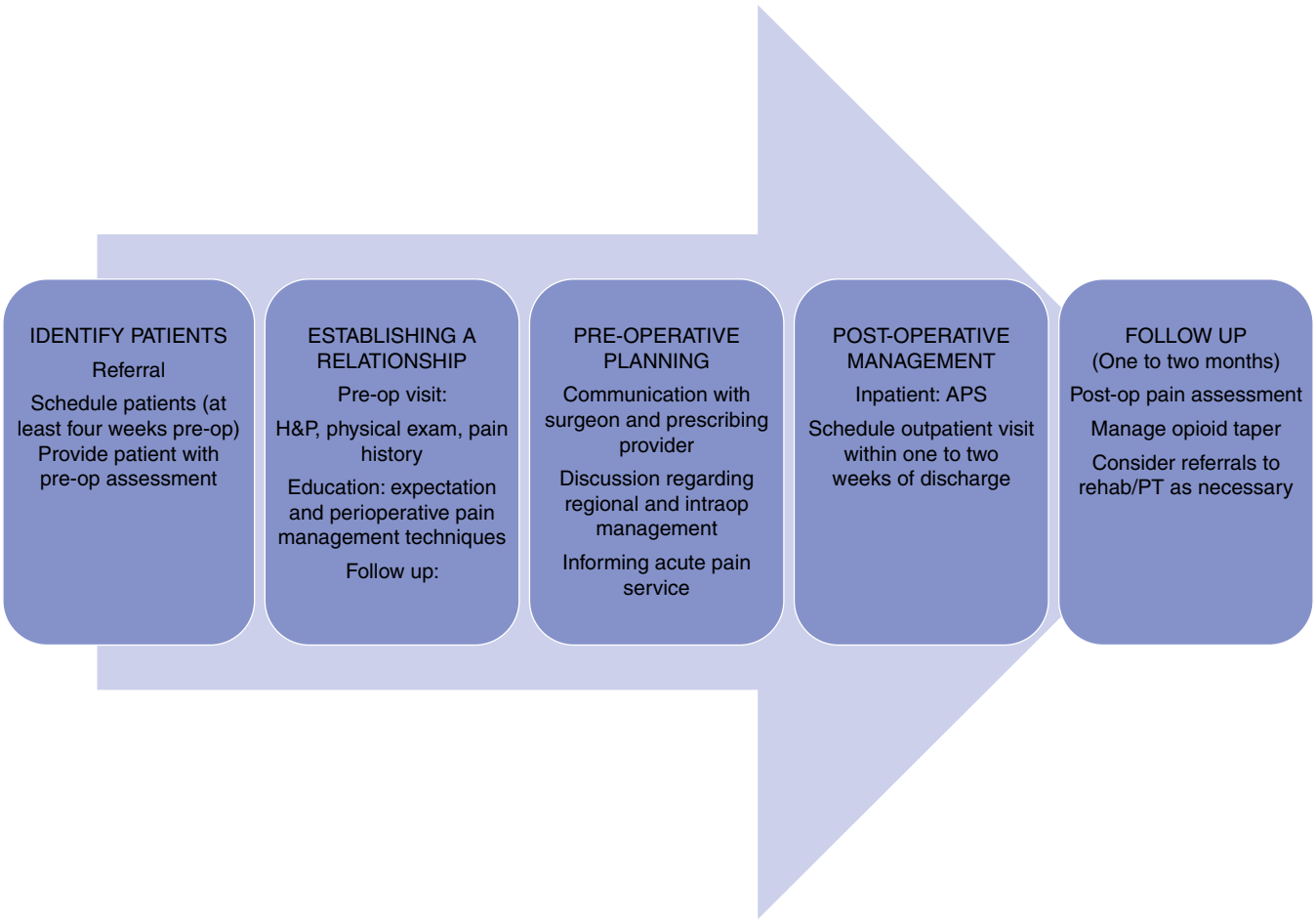
Institutional support for building perioperative pain services is mandatory. The benefits extend across departmental lines impacting surgical and anesthetic planning and treatment from pre-operative outpatient assessment and preparation, intraoperative management, post-operative inpatient care by all disciplines, and finally discharge and limited post-discharge therapy. As such, a perioperative pain clinic must be seen as an institutional resource or none at all. A multi-disciplinary approach is crucial in the development of perioperative pain services. Just as a multimodal approach to pain, using various pharmacologic and non-pharmacologic techniques is the standard of care for post-operative patients (allowing decreased reliance on opioids). The utilization of providers with different areas of expertise is crucial for perioperative pain management. Therefore caregivers from nursing, pharmacy, and pain medicine with close ties to surgery and anesthesiology will be needed to implement a successful perioperative pain service. Clinic patients should be those likely to have (1) post-operative pain that is difficult to control, (2) high dose post-operative opioid use requirements, and/or (3) risk factors for developing chronic pain after surgery, that is, largely mirroring the patients who already find their way into an inpatient acute pain service. At the University of Washington Medical Center, we used the following recommendations for patients undergoing inpatient surgery to be referred to the perioperative pain clinic:

- Pre-operative daily morphine equivalent dose of greater than 90 mg for three months
- Any daily opioid use > one year
- Use of daily extended release long-acting (ERLA) opioids for any length of time
- Patients on Suboxone (buprenorphine/naloxone)
- Patients on methadone
- Concurrent opioid and benzodiazepine use
- Known/active history of opioid use disorder (OUD) or other substance abuse
- History of difficult to control pain (for a similar type of surgery)

Surgeons should identify these patients as early as possible prior to scheduling surgery to allow for pre-operative assessment and interventions as needed. Ideally, the patient's pre-operative visit would include time with a pain provider, pain psychologist, and physical therapist to optimize evaluation and education. Specific evaluation should include risks of opioid misuse, psychological measures (including depression, anxiety, and catastrophizing), and functional disabilities, in addition to a thorough history of past pain problems and their treatment.

Perioperative pain clinic patient care should include (Fig. 3.6):

1. Intake (identify patients): Surgery referral; Schedule patient at least four weeks pre-operatively; Provide pre-visit assessment.
2. Visit (establish relationship): H&P focusing on pain history; assessment: including opioid risk tool, catastrophizing, and functional impairment testing; education and expectation management about post-operative pain and multimodal pain treatment: patient-provider agreement; communication with current pain provider, if any, and surgeon; form acute pain service +/- the regional anesthesia team; Start pre-operative medications if necessary.



• **Figure 3.6** Perioperative pain clinic patient flow.

3. Communicate with the inpatient social worker and/or pain psychologist if appropriate.
4. Group visit/education.
5. Intraoperative and post-operative care (therapeutic relationship): Relay intraoperative recommendations to the operative anesthetic team via acute pain service; Acute pain service follows as usual, including discharge recommendations; Schedule follow up with clinic if needed.
6. Follow up: Provide opioid therapy taper (two weeks- two months) in consultation with patients' pre-operative pain provider/prescriber; Consult with surgeons concerning referrals to physical therapy/occupational therapy and rehabilitation services.

Patients with past or current treatments with buprenorphine or methadone are prime examples of those who may benefit from pre-surgical consultation with the perioperative pain clinic. This is particularly true given the increase in medication-assisted treatment for OUD by the "opioid crisis" and the rapidly evolving literature on the management of these drugs in the perioperative period.[48,49,50]

Buprenorphine

Each patient on buprenorphine requires an individualized perioperative plan that should take the following into account: the reason they are on buprenorphine, the type of surgery and expected recovery period, the dose they are on, the social context, and access to appropriate providers available during the perioperative period. The literature on the management of buprenorphine pre- and postoperatively varies and is often contradictory. Various institutional protocols exist and continue to evolve as thinking and experience with buprenorphine evolves. For patients on buprenorphine, a well-constructed pain management plan is necessary to ensure safe and adequate post-operative pain control.[49]

The perioperative period can be very challenging for patients with OUD who are on maintenance therapy with buprenorphine. Pain can be more challenging to control, and they are at a high risk for relapse during this period. Patient education, coordination between providers, and detailed planning are necessary.

Key components in post-operative management for patients on buprenorphine:

1. The likely severity of post-operative pain is based on surgery type. For example, for outpatient surgeries with minimal post-operative pain anticipated, buprenorphine can and should be continued as is.
2. The reason patients were taking the medication: OUD vs. chronic pain. If the patient is taking buprenorphine for OUD, continuing daily dosing to avoid perioperative relapse (regardless of post-operative opioid tolerance).
3. Daily dose of buprenorphine: Consider outpatient tapering of doses >12 mg/day pre-operatively for surgeries expected to produce severe pain to avoid antagonism of full opioid

agonists (i.e. to avoid full μ-opioid receptor occupancy by the high doses of buprenorphine).
4. Collaboration between the patient, prescribing provider (pain/addiction specialist), and surgeon regarding the perioperative plan should always be done.

In general, past recommendations of completely discontinuing buprenorphine pre-operatively have fallen out of favor (particularly for normal starting doses of 18 mg/day or less).[51] As buprenorphine treatment at OUD doses has become more common, intravenous short-acting full opioid agonists (e.g. hydromorphone or fentanyl) have been reported to provide effective analgesia in the post-surgical setting while continuing buprenorphine, although with expected analgesic tolerance similar to patients treated preoperatively with other ERLA opioids.[52] Regional anesthetic techniques should be employed whenever possible and appropriate and non-opioid adjuncts in the post-operative period are of even greater value than usual in these patients. Discharge opioid medications also require careful coordination with the surgeon and outpatient buprenorphine prescriber with very close follow up within or separate from the perioperative pain clinic.

Methadone

As with buprenorphine, there are several reasons why patients might be on methadone, and there is a difference in approach to the patient on methadone maintenance therapy for OUD versus patients who are on methadone as an ERLA medication for chronic pain. In either group, the dose of methadone used for maintenance therapy is rarely adequate for treating any acute post-operative pain.[50] Therefore it is expected that such patients require higher opioid doses initially postoperatively. It is best not to chase such acute increases in pain with methadone. However, because of its long half-life and shorter onset, analgesics are preferable. As with buprenorphine, there is also an important role for post-operative regional anesthetic and multimodal pharmacologic treatments in these patients.

In patients with OUD, methadone maintenance is usually administered once a day to dampen cravings and ease dosing at methadone clinics. Pre-operatively, every effort should be made to ensure that the patient's OUD treatment program is aware of upcoming surgery if it will mean an inpatient hospital stay. It is recommended that patients either coordinate to obtain their daily dose from their maintenance program or receive their normal oral dose separately pre-operatively on the day of surgery.

For acute post-operative pain, methadone dosing, whether administered pre-operatively for OUD or pain, should be administered in divided doses (every 6 or 8 h at the same total daily dose) to optimize its analgesic window. If the patient is kept strictly NPO, consider administering methadone IV to avoid long "wash-in" times when restarting methadone. Although this is admittedly conservative with the high bioavailability of oral methadone, we used an intravenous dose equal to half the calculated oral dose. This IV methadone dose, nonetheless, keeps blood levels from falling too dramatically and certainly avoids withdrawal symptoms as supplemental short-acting opioids are always provided (usually by IV PCA) for breakthrough pain in the post-operative period.[53] The goal should be to taper off short-acting opioids in the subacute post-operative period (no more than six weeks and usually much less) as appropriate recovery, and for tissue healing to occur. As short-acting opioid use diminishes, the patient should then be returned to their methadone dosing once a day if they remain hospitalized, or a follow up appointment should be coordinated with the outpatient maintenance program upon discharge. Guidance from an addiction specialist or the patient's maintenance program can help inform decisions on discharge medications.[54]

A Different Kind of Service

An ironic advantage of the tragic "opioid crisis" that has gripped North America (and to a lesser extent the rest of the world), costing many thousands of lives, is an increase in interest in the appropriate management of pain. This is because the opioid crisis is not so much a "problem" as it is a "dilemma"—less in need of a solution (like banning all opioids) as it is a management strategy. Thus, agencies, commissions, societies, and institutions that would never have shown any interest in pain treatments in the 20th century are suddenly publishing opioid prescribing guidelines—the best of which (for example, the Centers for Disease Control and Prevention [CDC] guidelines),[55] when examined closely, are really pain management guidelines. As mentioned earlier, the fight to discard the notion that "pain management" equals "opioid therapy" is still rampant—a fight that, at its core, is probably the primary "raison d'etre" for the development and existence of pain services. As a result, leaders of an inpatient acute pain service will now have a huge opportunity to teach other medical professionals about pain assessment and management skills that they never had before, even though pain management specialists may have been practicing these skills for decades.

ERAS Opportunities

These teaching opportunities are no longer confined to lectures at Grand Rounds or trainee didactics. Educators in other departments or professions may reach out to pain service leaders, asking them to allow their trainees to spend time on the pain service. In our service, the visitors to rounds from around the world (common in the 1990s) have been replaced by nursing, nurse practitioners, physician assistants, pharmacy students, and even residents from other medical disciplines within the institution, though not yet from surgery. On the other hand, long overdue interest in post-operative pain management among surgeons has also grown rapidly with skyrocketing protocols and guidelines appearing in the literature on appropriate durations of post-operative opioid prescription; for example,[42,56,57] Perhaps the most useful resource in this regard for evidence based procedure specific data on opioid use after surgery is the Michigan Opioid Prescribing and Engagement Network (OPEN)and their website (https://michigan-open.org/prescribing-recommendations/). In combination with knowledge of the PROSPECT recommendations mentioned earlier,[32] concerning evidence based pain treatments found to reduce pain and improve function after specific surgeries—and their own experiences, pain service leaders can be a valuable resource as additions to committees crafting their institution's ERAS protocols. Although one could conceivably argue that this might negatively impact consult volume and thus billing, a role in developing ERAS protocols gives pain service leaders an influence, never before possible, on the pain and opioid risks of inpatients and outpatients with surgery who would never have come to our service anyway and at the same time improve the quality and efficiency of our colleagues and health care systems.

Opioid Stewardship Activities

Another recent teaching opportunity for acute pain team members seeking to improve institutional pain management is involved in opioid stewardship activities. Modeled on hospital antibiotic

stewardship programs required by the JCAHO, opioid stewardship is described by the Canadian Institute for Safe Medication Practices as "coordinated interventions designed to improve, monitor and evaluate the use of opioids to support and protect human health."[58] It is hard to imagine professionals who are better positioned to be involved in these efforts than acute pain service leaders. By definition, opioid stewardship is a multi-disciplinary and multi-professional endeavor (drawing on pharmacy, nursing, surgical, primary care, emergency medicine, pain medicine, and addiction medicine expertise), and again, acute pain service leaders, by necessity, are experienced in such endeavors. If your institution has not yet implemented an opioid stewardship committee, you can be assured that one is planned as JCAHO has already gone on record as supporting such initiatives.[59] More and more case studies of institutional programs are being published, and the National Quality Forum has suggested seven fundamental steps needed to support opioid stewardship in health care organizations:[60, 61]

- Promote leadership commitment and culture.
- Implement organizational policies.
- Advance clinical knowledge, expertise, and practice.
- Enhance patient and family caregiver education and engagement.
- Track, monitor, and report performance data.
- Establish Accountability.
- Support community collaboration.

In our system, the opioid stewardship committee is a subcommittee of the pharmaceutics and therapeutics committee and provides part-time administrative support for our monthly meetings. We used a workgroup approach to underpin the complex and far-reaching activities of the opioid stewardship committee. These workgroups have evolved over the years and will continue to do so, but currently include addiction services, education, metrics, and documentation groups—all held together by invaluable information technology support for each group (without which, in this day and age, would make most of the work of the committee impossible). As with most committees, most of the time is spent by a handful of dedicated individuals composing the leadership team. This currently comprises the chairs of the various workgroups as well as the two co-chairs of the larger opioid stewardship committee (a pain specialist and an addiction specialist). As it happens, many of our leaders are active in advocacy work at the state and national levels, including the development of several opioid-related rules and guidelines. However, this is neither necessary nor sufficient. The goal of opioid stewardship activities, as is the case with most pain service activities, is implementing local policies and procedures to help ourselves and our colleagues more safely care for our patients in an evidence based more efficient, and more effective manner.

Conclusion

Although healthcare providers acknowledge that providing analgesia to acute post-surgical patients is important, this task is often easier said than done. Challenges to meeting this aim include opioid tolerance, acute-on-chronic pain scenarios, and a great variety of surgical procedures and techniques. An acute inpatient pain service can often offer insight and experience when dealing with complex clinical issues. However, the design, planning, and implementation of an acute inpatient pain service must be performed with great care, and intention with an eye toward flexibility as pain problems and solutions evolve. Only through thoughtful construction will a successful service emerge that can meet and exceed the needs of the hospital, its surgical and medical services, and the patients whom they serve.

Key Points

- Acute post-operative pain remains widely undertreated, even though it is a primary concern for patients anticipating planned surgery.
- An optimal post-operative pain management program will integrate multimodal and multi-disciplinary interventions.
- Several systems for organizing an inpatient acute pain service have been described, although most use a partnership between nursing and anesthesiology.
- Detailed practice guidelines, protocols, and order sets can streamline and simplify care.
- Enlisting the support of hospital administration and defining resources is a vital first step in organizing an inpatient acute pain service.
- Treatments provided by the pain service should be individualized and evidence based.
- The business plan of the service must include a cost analysis, although the delivery of pain relief is inherently valuable beyond a calculable measure.
- The business plan should be flexibly constructed by shifting fixed costs to variable costs whenever possible.
- Accuracy in documentation and billing is crucial to facilitate timely and correct reimbursement.
- A marketing plan introduces potential referring providers to the concept and benefits of the service.
- Flexibility for improving pain care based on technologic innovations, health systems, or regulatory changes related to pain is essential for providing long-term, safe, and efficient pain care.

Suggested Readings

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The references for this chapter can be found at ExpertConsult.com.

Appendix A

History

HPI (history of present illness): Characterize HPI by considering either the status of chronic conditions or the number of elements recorded. ☐ One condition ☐ Two conditions ☐ Three conditions or ☐ Location ☐ Severity ☐ Timing ☐ Modifying factors ☐ Quality ☐ Duration ☐ Context ☐ Associated signs and symptoms	☐ Status of one to two chronic conditions	☐ Status of one to two chronic conditions	☐ Status of three chronic conditions	☐ Status of three chronic conditions
	☐ Brief (one to three)	☐ Brief (one to three)	☐ Extended (four or more)	☐ Extended (four or more)
ROS (review of symptoms) ☐ Constitutional (weight loss) ☐ Ears, nose, mouth, throat ☐ GI ☐ Integumentary (skin, breast) ☐ Endo ☐ Eyes ☐ Cardiovasc ☐ GU ☐ Musculo ☐ Neuro ☐ Me/lymph ☐ Resp ☐ Psych ☐ All/immuno ☐ Psych	☐ N/A	☐ Pertinent to problem (one system)	☐ Extended (Pert and others) (two to nine systems)	☐ Complete (Pert and all others) (ten systems)
PFSH (past, family, social history) ☐ Past history (the patient's past experiences with illnesses, operations, injuries, and treatments) ☐ Family history (a review of medical events in the patient's family, including diseases that may be hereditary or place the patient at risk) ☐ Social history (an age-appropriate review of past and current activities)	☐ N/A	☐ N/A	☐ Pertinent (one history area)	☐ *Complete (two or three history areas)
*Complete PFSH: two history areas: (a) established patients—office (outpatient) care, domiciliary care, home care; (b) emergency department; (c) subsequent nursing facility care; and (d) subsequent hospital care three history areas: (a) new patients—office (outpatient) care, domiciliary care, home care; (b) consultations; (c) initial hospital care; (d) hospital observation; and (e) initial nursing facility care	Problem focused	Exp. problem focused	Detailed	Comprehensive
	Final history requires all three components above met or exceeded			

Appendix B

Examination			
CPT Examination Description	**1995 Guideline Requirements**	**1997 Guideline Requirements**	**CPT Type of Examination**
Limited to affected body area or organ system	One body area or organ system	One to five bulleted elements	Problem focused examination
Affected body area or organ system and other symptomatic or related organ systems	Two to seven body areas and/or organ systems	Six to 11 bulleted elements	Expanded problem focused examination
Extended examination of affected body area or organ system and other symptomatic or related organ systems	Two to seven body areas and/or organ systems	12–17 bulleted elements for two or more systems	Detailed examination
General multisystem	Eight or more body areas and/or organ systems	18 or more bulleted elements for nine or more systems	Comprehensive examination
Complete single-organ system examination	Not defined	See requirements for individual single-system examinations	

CPT, Current Procedural Terminology.

Appendix C

Data Reviewed or Ordered		Point Value
Order and/or review medically reasonable and necessary clinical laboratory procedures. Note: Count laboratory panels as one procedure.	One to three procedures	1
	≥ Four procedures	2
Order and/or review medically reasonable and necessary diagnostic imaging studies in the radiology section of CPT.	One to three procedures	1
	≥ Four procedures	2
Order and/or review medically reasonable and necessary diagnostic procedures in the medical section of CPT.	One to three procedures	1
	≥ Four procedures	2
Discuss tests results with the performing physician.		1
Discuss the case with other physicians involved in the patient's care or consult another physician (i.e. true consultation meaning seeking opinion or advice of another physician regarding the patient's care). This does not include referring the patient to another physician for future care.		1
Order and/or review old records. Record type and source must be noted. Review of old records must be reasonable and necessary based on the nature of the patient's condition. Practice or facility protocol-driven record ordering does not require physician work and thus should not be considered when coding E/M services. Perfunctory notation of old record ordering/review solely for coding purposes is inappropriate, and counting such is not permitted.	Order/review without summary	1
	Order/review and summarize	2
Independent visualization and interpretation of an image, ECG, or laboratory specimen not reported for separate payment. Note: Each visualization and interpretation is allowed one point.		1
Review of significant physiologic monitoring or testing data not reported for separate payment (e.g. prolonged or serial cardiac monitoring data not qualifying for payment as rhythm ECGs).		1
	Total points	

CPT, Current Procedural Terminology; *ECG*, electrocardiogram; *E/M*, evaluation and management.

Appendix D

Risk for Complications and/or Morbidity or Mortality			
Level of Risk	**Presenting Problem(s)**	**Diagnostic Procedure(s) Ordered**	**Management Options Selected**
Minimal	One self-limited or minor problem, e.g. cold, insect bite, tinea corporis	Laboratory test requiring venipuncture Chest x-rays ECG/EEG Urinalysis Ultrasound, e.g. echocardiography KOH preparation	Rest Gargles Elastic bandages Superficial dressings
Low	Two or more self-limited or minor problems One stable chronic illness, e.g. well-controlled hypertension or non-insulin dependent diabetes, cataract, BPH Acute uncomplicated illness or injury, e.g. cystitis, allergic rhinitis, simple sprain	Psychological test not under stress, e.g. pulmonary function tests Non-cardiovascular imaging studies with contrast, e.g. barium enema Superficial needle biopsies Clinical laboratory tests requiring arterial puncture Skin biopsies	Over-the-counter drugs Minor surgery with no identified risk factors Physical therapy Occupational therapy IV fluids without additives
Moderate	One or more chronic illnesses with mild exacerbation, progression, or side effects of treatment Two or more stable chronic illnesses Undiagnosed new problem with an uncertain prognosis, e.g. lump in the breast Acute illness with systemic symptoms, e.g. pyelonephritis, pneumonitis, colitis Acute complicated injury, e.g. head injury with brief loss of consciousness	Physiologic tests under stress, e.g. cardiac stress test, fetal contraction stress test Diagnostic endoscopy with no identified risk factors Dee needle or incisional biopsy Cardiovascular imaging studies with contrast and no identified risk factors, e.g. arteriogram, cardiac catheter Obtain fluid from the body cavity, e.g. lumbar procedure, thoracentesis, culdocentesis	Minor surgery with identified risk factors Elective major surgery (open, percutaneous, or endoscopic) with no identified risk factors Prescription drug management Therapeutic nuclear medicine IV fluids with additives Closed treatment of fracture or dislocation without manipulation
High	One or more chronic illnesses with severe exacerbation, progression, or side effects of treatment Acute or chronic illnesses or injuries that may pose a threat to life or bodily function, e.g. multiple trauma, acute MI, pulmonary embolus, severe respiratory distress, progressive severe rheumatoid arthritis, psychiatric illness with a potential threat to self or others, peritonitis, acute renal failure An abrupt change in neurologic status, e.g. seizure, TIA, weakness, or sensory loss	Cardiovascular imaging studies with contrast Cardiac electrophysiologic tests Diagnostic endoscopy with identified risk Diskography	Elective major surgery (open, percutaneous, or endoscopic) with no identified risk factors Emergency major surgery (open, percutaneous, or endoscopic) Parenteral controlled substances Drug therapy requiring intensive monitoring for toxicity Decision not to resuscitate or to de-escalate care because of poor prognosis

BPH, Benign prostatic hyperplasia; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *IV*, intravenous; *MI*, myocardial infarction; *TIA*, transient ischemic attack.

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4

Interdisciplinary Pain Management

STEVEN P. STANOS

"Chronic pain is a complex biopsychosocial phenomenon that may interfere with many aspects of a person's life—ability to work, personal relationships, and both physical and mental health".[1]

The National Pain Strategy

"Pain for me, arrives as a complete package, and that demands a team approach."

Patrick Wall, PhD

Introduction

Interdisciplinary pain rehabilitation incorporates a team-based approach based on a biopsychosocial model of care. This chapter will review the history of multi- and interdisciplinary care, functional restoration, and the various treatment disciplines involved that contribute to the success of chronic pain rehabilitation programs. The chapter will review the author's interdisciplinary program in the Pacific Northwest as an example and means for a deeper discussion of program philosophy, workflow, and processes. This section also highlights additional federal, academic, and private programs across the United States, including recent outcomes studies. This overview of interdisciplinary care will help represent where a strong interdisciplinary pain rehabilitation model can be integrated into a traditional comprehensive pain center at a healthcare system level or as an independent freestanding entity. Most importantly, an explanation of specific therapeutic disciplines and treatment focus provided by physical therapy (PT) and occupational therapy (OT), pain psychology, relaxation training (RT), medical management, and pain education will be reviewed along with the unique synergies a team-based approach provides helping patients struggling to manage chronic pain decrease their pain and suffering, better understand their condition, and improve psychosocial function and quality of life.

History of Pain Rehabilitation

Pain rehabilitation and treatment of injured workers go back to the Egyptians under Ramses II in 1500 BD. The modern development of more formal rehabilitation models of care evolved after both World Wars, with the birth and advancements in the fields of rehabilitation medicine and OT. The advancement of various medical specialties and health psychology helped advance further growth in the mid-twentieth century. Dr. John Bonica championed a "multi-disciplinary" approach and formalized a consultation-based program in the early 1960s at the University of Washington.[2] Patients were assessed by a multi-disciplinary group of providers, discussed in a multi-disciplinary manner where patient specific treatment plans and recommendations were made. Over time, the consultation-based multi-disciplinary clinic has evolved into providing more structured inpatient programs in collaboration with anesthesia, physical medicine and rehabilitation, and health psychology. Wilbert Fordyce, a psychologist and early leader in the field of behavioral medicine, joined Bonica and applied operant conditioning and behavioral interventions in what was initially an inpatient eight week program. Fordyce had a primary interest in operant conditioning principles that shape both pain-related and healthy behaviors, noting several learned processes that maintained "pain behaviors," those behaviors that can be positively and negatively reinforced.[3] The approach was a sharp contrast to the more contemporary practiced biomedical model, which emphasizes physiologic pathology shifting to a more comprehensive and patient-centered "biopsychosocial" approach. The biopsychosocial model, championed by George Engel, has been used to treat medical conditions, including cardiovascular and gastrointestinal disorders and infectious diseases.[4]

In 1983 John Loeser and Bill Fordyce at the University of Washington formalized a more "structured program," three weeks in duration, that become a model of "interdisciplinary" treatment around the word.[5] In Texas, Mayer and Gatchel in the 1970s and 1980s incorporated "functional restoration" into the interdisciplinary model to better address deconditioning and prolonged disability associated with low back pain with injured workers. The interdisciplinary functional restoration approach focused on physical reconditioning and cognitive behavioral "crisis intervention" for helping patients manage related psychosocial problems.[6] The functional restoration model grew from a sports medicine approach to work related injuries focusing on endurance training and strengthening. Along with cognitive behavioral support and didactic teaching about the nature of pain, pain management principles, and disability avoidance, functional restoration programs are also highly interdisciplinary, with a focus on the progressive increase in levels of task-oriented rehabilitation and work simulation, with ongoing objective and functional assessments.

These interdisciplinary functional restoration programs have been shown to improve pain and function and improve spine surgical outcomes when integrated as a "prehabilitation" intervention prior to surgery.[7] Over time, "interdisciplinary treatment" and "functional restoration" have become terms synonymous with structured rehabilitation-based programs. Okifuji et al. described

three common elements of interdisciplinary treatment, including medication management, graded physical exercises, and cognitive and behavioral techniques for pain and stress management.[8]

With a strong emphasis on interdisciplinary care, pain program treatment facilities grew in the 1980s and the 1990s worldwide, including in the United States. Accreditation by the Commission on Accreditation of Rehabilitation Facilities (CARF) and other organizations led to the growth of these programs in the United States, many of which focused on rehabilitating injured workers and returning them to work. Unfortunately, despite evidence of interdisciplinary treatment efficacy, a significant decline in CARF accredited programs began in the early 2000s. However, in the federal health system, the availability of these programs grew significantly in 2009 because of the Veterans Health Administration (VHA) Directive in response to the growing opioid epidemic and an increase in the prevalence of chronic pain.[9] The directive outlined a new standard of multimodal pain care at all levels of clinical care by formally establishing a more seamless population-based, patient-centered, stepped care model of pain management. The model includes "Step One: Primary Care," "Step Two: Secondary Consultation," and "Step 3: Tertiary Interdisciplinary Care" with Step 3 helping to better the needs of more complex patients requiring advanced pain medicine diagnostics and pain rehabilitation.[10]

In 2011, the Agency for Healthcare Research and Quality (AHRQ) published a technical brief on multi-disciplinary pain programs, which included reviews of interdisciplinary programs describing programs that provide medical therapy, behavioral therapy, physical reconditioning, and education. The AHRQ report reviewed the literature on the positive efficacy of interdisciplinary care and described the growth of programs in Europe while declining the number of programs in the United States.[11] Efforts to curb the growing drug overdose epidemic and increased reported prevalence of chronic pain and high-impact chronic pain have led to greater support for comprehensive pain care, including interdisciplinary care. In the near future, the development of value-based care models and payer systems in the United States healthcare system may offer an opportunity for greater integration of a continuum of team-based approaches to improve comprehensive pain care. An interdisciplinary care model is the foundation of this care system.

Legislative and Federal Initiatives Highlighting the Need for Interdisciplinary, Team-Based Care

Initiatives and legislative acts supporting multi- and interdisciplinary care include the National Pain Strategy, the Centers for Disease Control and Prevention (CDC) Chronic Opioid Management Guideline,[12] the National Academies of Medicine report,[13] Health and Human Services (HHS) Pain Management Interagency Task Force report,[14] and National Governor's Association report.[15]

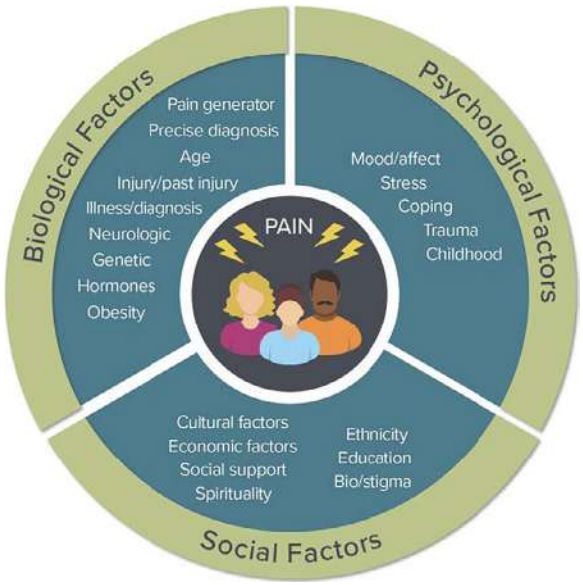
The 2010 Patient Protection and Affordable Care Act (ACA) required the Secretary of HHS to coordinate through the Institute of Medicine (IOM) a strategy to increase awareness and recognition of pain as a significant public health problem. The IOM report included several recommendations for improvements in pain spanning data collection, education, research, and delivery of care, leading to a congressionally mandated federal effort into a comprehensive population health-level strategy, the National Pain Strategy (NPS). The NPS, released in 2017, and endorsed "a population-based, biopsychosocial approach to pain care that is grounded in scientific evidence, integrated, multimodal, and interdisciplinary while, at the patient level, is tailored to individual needs." The NPS lays the foundation for greater integration of team-based interdisciplinary care and better delivery strategies and integrates this type of care into current treatment models, payers, and healthcare systems. The report included definitions that will help guide this overview of interdisciplinary care.[12] The ACA, which increased access to medical coverage for the uninsured, has also helped to support the growth of interdisciplinary and comprehensive care within state Medicaid systems, including novel team-based programs that may help to more widespread use of programs within Medicare and commercial payor programs.

The National Academy of Sciences and the HHS Interagency Task Force report emphasized a multi-disciplinary approach based on a biopsychosocial model and included an endorsement of multi-disciplinary care as a critical part of biopsychosocial-based care. Besides behavioral health approaches, interventional procedures, medications, and complementary and integrative health, the range of restorative therapies (physical and OT, therapeutic exercise, and movement modalities) are critical components of interdisciplinary, multimodal pain care.[13,14]

As shown in Figure 4.1, response to the drug overdose epidemic highlighted the need for states to examine current evidence, coverage, and access for non-opioid therapies and explore innovative, coordinated, interdisciplinary care delivery models "that function as best practice models for patients experiencing complex high-impact chronic pain."[15] In 2020 the National Governor's Association report addressed strategies to expanding access to non-opioid pain management in the context of the COVID-19 pandemic. The report also highlighted progress in several states through waivers, health home programs, and performance improvement projects to promote evidence-based non-opioid therapies, including interdisciplinary rehabilitation, and improve how chronic pain is addressed in primary care.[16]

Models of Care

A few important definitions are reviewed to describe the models of care. The terms "multi-disciplinary" and "interdisciplinary" as models of care are commonly used interchangeably, although they



• **Figure 4.1** Biopsychosocial factors impacting pain. HHS: Interagency Task Force report. 2019.

represent treatment models across a continuum of care in modern clinical practice. Heterogeneity in the terminology used to describe pain management programs in the literature may lead to some confusion. "Multi-disciplinary" implies multiple disciplines being used for a clinical purpose but not necessarily delivered in one setting. "Interdisciplinary" implies the use of multiple disciplines, such as occupational and PT, behavioral medicine, RT, vocational services, and nursing education in one setting or facility.[17]

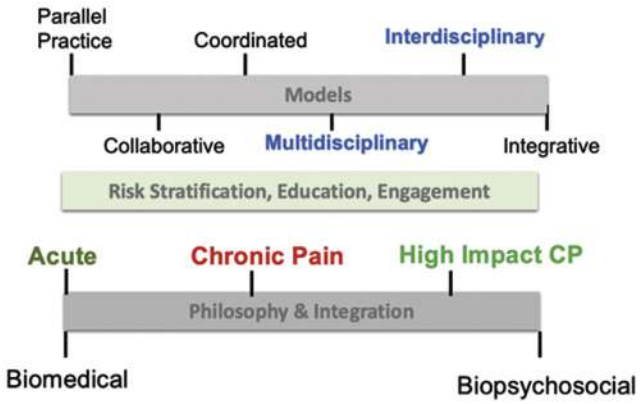
Boon et al. described a conceptual framework of models of care in order of increasing comprehensiveness and philosophical complexities, starting with a more biomedically based model parallel to a collaborative, coordinated care. This is followed by a multi-disciplinary, then interdisciplinary biopsychosocial model, and finally, a fully integrative one,[18] which could include acute medical care, such as an emergency room, where different team members have defined roles (i.e. phlebotomy, nursing, radiology technician, and emergency medicine provider). A "collaborative" or "coordinated" model may include practitioners acting independently and sharing medical records facilitated by a case manager. Across the models, there is an increasing need for communication, less individual autonomy, increased goals, and shared philosophy. "Multi-disciplinary" in pain management may commonly include a patient being managed by a pain medicine specialist who is directing care, a physical therapist providing care at an outside facility, and a vocational counselor working with the patient individually. At an even higher level of integration, "interdisciplinary" care, a basic tenet of functional restoration, includes multiple disciplines providing care at one facility. This is often led by a pain management specialist or behavioral health specialist, with multiple allied health disciplines (physical and OT, behavioral health [pain psychology, counseling, social work], nursing education) working together, agreeing upon treatment goals, and ongoing active communication, including formal team conferences or meetings. Integrated pain management programs are centered in and integrated into primary care with some embedded or easy access to multi-disciplinary providers and services. This arrangement has been described primarily in the federal healthcare system, including the Veterans Administration and the Department of Defense. This continuum starts with a more biomedical, pathology-focused approach, progressing to more multi-disciplinary, then interdisciplinary and integrative models more heavily dependent on a biopsychosocial team-centered approach. The continuum and progression in philosophy can similarly be appropriate for how a person with pain is treated, starting with acute pain, chronic pain, and finally high-impact chronic pain, but all models equally consider individual patient risks, values, engagement, education, and knowledge (Figure 4.2). The following important definitions better define the population and scope of treatment:

High-impact chronic pain: Pain associated with substantial restrictions on participation in work, social, and self-care activities for six months or more

Integrated care: The systematic coordination of medical, psychological, and social aspects of healthcare includes primary care, mental health, and, when needed, specialist services.

Interdisciplinary care: Care is provided by a team of health professionals from diverse fields who coordinate their skills and resources to meet patient goals.

Multimodal pain treatment: Addresses the full range of an individual patient's biopsychosocial challenges by providing a range of multiple and different types of non-pharmacologic (active therapy, behavioral health, interventional procedures) and pharmacologic therapies as needed.



• **Figure 4.2** Models of care, philosophy, and biomedical to biopsychosocial continuum. Adapted from Boone, et al.

Continuum of Care: Pain Rehabilitation

A continuum of pain rehabilitation approaches for chronic pain can include various models, including back schools, primary care integrative programs, and interdisciplinary functional restoration. A consistent emphasis on education and self-management was seen at varying levels with these approaches. A brief description of these models helps put into context the most comprehensive pain rehabilitation continuum, interdisciplinary care.

Back Schools

Back schools have been defined as interventions that include group education, training, and exercise, often delivered by a physical therapist or other healthcare provider organized in an occupational setting or part of a multi-disciplinary treatment program. Programs include brief education by a single provider within a management-based group. Back schools encourage self-management, advice to stay active, and reduce potential concerns about low back pain.

Low back pain education programs were championed by Lidstrom, Zachrisson, and Forsell in the late 1960s as the "Swedish Back School" model. Swedish back school classes focus specifically on biomechanics, ergonomics, exercise, and skill acquisition.[19,20] Studies have demonstrated efficacy in treating low back pain.[21] The content of back schools has varied over time, and endorsement of these programs in treatment guidelines has waned. Recent reviews found limitations, including insufficient studies and low quality evidence, although more effective than placebo on work status, and may be more effective as an added treatment versus provided alone.[22] Other reviews have demonstrated conflicting evidence that schools are better than waiting lists or no intervention for reducing disability or improving return to work.[23]

Integrative Primary Care

Collaborative care models for chronic pain, conceptually based on treating chronic illnesses such as diabetes and depression, based on primary care have demonstrated efficacy.[24,25] Focus areas for collaborative care for chronic pain include patient identification and population management, a defined care team with access to specialty pain and behavioral health with standard workflows and system supports, coordinated and collaborative care management,

and evidence-informed care (that is trauma-informed, addressing pain amplifiers like sleep problems, appropriate use of integrative health such as massage and acupuncture, and movement and body awareness strategies). Finally, patient-supported self-management is provided by a team member where goals are identified, and barriers to making progress toward goals are addressed (Table 4.1).[26]

Primary care-based integrative pain management programs are often based on medical home models. Various primary care models exist but often include coupling a decision-support component such as an algorithm-guided treatment (such as analgesic optimization) or stepped care with proactive treatment monitoring, stratifying patients based on the extent of their medication management, psychosocial, and/or comorbid medical illness factors. Programs are commonly led by case managers who communicate with patients via phone or other automated symptom monitoring (apps, internet). Education was delivered in multiple weekly group sessions. In some cases, primary care-based integrated programs also include physicians, pharmacists, dieticians, and physical therapists who provide group or individual care. A recent review of primary care models found clinically relevant improvements in pain intensity and function, with variable improvement in other core outcomes such as mood, sleep, and medication use.[27] Additional trials are ongoing with the integration of interdisciplinary pain care within primary care, including models that include comprehensive evaluations, cognitive behavior therapy (CBT)-based pain coping skills training, and adaptive movement training provided over a 12-week period in group sessions (led by a trained nurse and behavioral specialist), and primary care consultation.[28]

Interdisciplinary Pain Rehabilitation and Functional Restoration

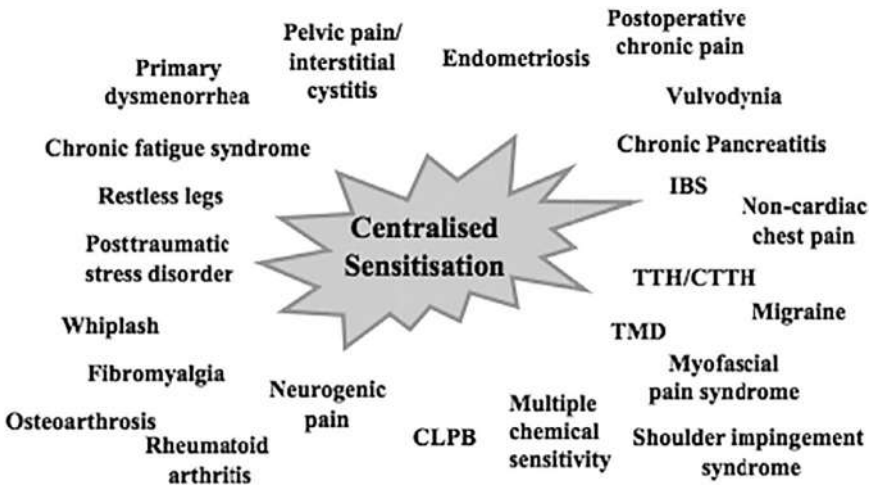
Interdisciplinary models are based on a biopsychosocial approach to pain and pain-related loss of function (i.e. disability). The biopsychosocial approach emphasizes pain and disability as complex and dynamic interactions among physiologic, psychological, and social factors that may perpetuate each other, leading to complex pain and prolonged disability.[29] Importantly, in contrast to a biomedical model, chronic pain is understood as a disease, making the traditional biomedical model often inadequate at addressing the complexities of pain unique to each patient.[30] The evidence for interdisciplinary pain rehabilitation programs as effective interventions for reducing pain and pain-related disability is well established in the literature.[31,32,33]

Important in this complex biopsychosocial relationship underscoring pain and affective distress is evidence supporting neurophysiologic changes, including neurophysiologic activation, and more recent evidence of chronic pain perpetuating central sensitization. Central sensitization has been defined as "a process of abnormal and intense enhancement of pain caused by increased neuronal responses to stimuli in the central nervous system."[34,35] Central sensitization is associated with psychosocial and cognitive behavioral factors.[36] Central sensitization plays an important role across many chronic pain conditions and contributes to the transition process from acute to chronic pain, amplification of pain in many chronic pain conditions, and in the development of chronic post-operative pain (Figure 4.3).[37]

TABLE 4.1 Primary Care Collaborative Care for Chronic Pain Focus Areas (Bree Collaborative)

Patient Identification and Population Management	• Identifying patients with persistent pain with life activity impacts • Preventing the transition from acute to chronic pain with life activity impacts • Through screening with a brief, validated instrument for psychosocial barriers • To recovery (e.g. STarT Back Tool for low back pain) • Tracking patients in a registry and participating in performance improvement • Based on the aggregation of data for collaborative care performance • Use of a dashboard for patient progress • Patient-reported outcome measures at the initial visit and follow up
Care Team	• Defined roles for care team members, care team • Communication expectations • Access to specialty pain or behavioral health consultation, if needed • Patient point of contact for the care team • Standard workflow with planned interactions • System supports (e.g. technology, training) • Identifying, supporting, and enhancing what patients are already doing to manage chronic pain with life activity impacts
Care Management	• Coordination of the collaborative care process, including facilitation of care team access • Identifying diverse resources and interventions that patients can use in managing chronic pain with life activity impacts, depending on motivations and preferences • Facilitation of referrals, if needed • Management of medication • Proactive outreach
Evidence-Informed Care	• Trauma-informed care • Developing and improving pain management skills (e.g. relaxation) • Conventional medical treatment options (e.g. nonsteroidal anti-inflammatory drugs as first line treatment rather than opioids, topical, heat, and ice) • Addressing pain amplifiers (e.g. sleep problems) • Integrative health practices (e.g. massage, acupuncture) • Movement and body awareness strategies
Supported Self-Management	• Helping patients identify goals for resuming life activities and addressing barriers to making progress toward goals

Collaborative care for chronic pain: report and recommendations. *Bree Collab*. 2018.



• **Figure 4.3** Chronic pain conditions and central sensitization.[37]

In addition to sensitization, neurophysiologic changes may be closely linked to psychological and behavioral factors. The classic cognitive activation theory of stress links neurophysiologic activation and an individual's innate stress alarm, where there is a discrepancy between what is expected and experienced by the individual with chronic pain.[38] The resulting sustained state of anxiety and sustained neurophysiologic activation may be reduced by improved coping behaviors or decreasing feelings of hopelessness. Many of these related psychological factors are targets for fear avoidance training for persistent pain. Sensitization to pain processing also contributes to elevated pain perception and affective distress. Decreasing "sensitization" of the nervous system serves as a useful broad or shared target for pharmacologic, behavioral, and active non-pharmacologic interventions (exercise, movement-based therapies) for pain management. It remains an important and growing area of clinical focus and patient-directed education within interdisciplinary and multidisciplinary treatments.

Interdisciplinary Care and Functional Restoration

Over 30 years ago, Kinney et al. described the basic elements (i.e. nine core attributes") of interdisciplinary functional restoration programs.[6] With advancements in understanding persistent pain, pain pharmacology, health psychology, and integration of mind body techniques, these nine core attributes remain, but with updated modifications. These nine core attributes will help describe the continuum of interdisciplinary care (Table 4.2).

Interdisciplinary functional restoration can be best described as involving four phases:

1. Comprehensive interdisciplinary assessment: Multiple specialists (pain medicine, pain psychologist, and/or vocational counselor) evaluate the patient, help clarify the underlying pain and psychological diagnoses, and consider candidacy for interdisciplinary care.
2. Pre-programing: Pre-programing as needed to complete workup, complete related assessments, and/or stabilize psychiatric or medical issues and program orientation.
3. Formal interdisciplinary management.
4. Post-program: Follow up care, outcome assessments, and maintenance classes.

TABLE 4.2 Core Attributes of a Functional Restoration Program: Swedish Pain Services/Swedish Health System)

1. Pain medicine assessment and management: Review of past treatment, diagnostic workup, comprehensive musculoskeletal, neuromuscular examination, assessment of neuropathic, nociceptive, and nociplastic pain; discussion with the patient regarding treatment plan; rationale for treatment program specific to patient needs; and ongoing visits reviewing progress.
2. Pain Psychology Evaluation and Treatment; psychosocial functioning: semi-structured pain psychology assessment, completion of psychosocial packet questionnaires.
3. PT directed reconditioning, strengthening, stabilization, and wellness, and pain education, many times including a model based on PNE.
4. OT directed work and home physical functioning assessment, pacing and ergonomic training, integration of relaxation techniques and mindfulness, Tai Chi, and Qi Gong training.
5. Behavioral health, including pain psychology and RT CBT, mindfulness, acceptance and commitment therapy (ACT) approaches, biofeedback-assisted RT, and nervous system education.
6. Pharmacologic interventions targeting analgesia, mood, and sleep, including detoxification or opioid tapering when appropriate, medication trials, and medication optimization, are usually led by a pain medicine specialist, physiatrist, and psychiatrist.
7. Interdisciplinary, medically-directed team approach with formal weekly team conference meetings, including structured report generation from all disciplines.
8. Work and avocational reintegration guided by nurse educators, pain medicine specialists, OT, PT, and behavioral health teams include a return to work plan, work release, and flare up management.
9. Ongoing outcomes assessments.

The intensity of treatment, disciplines involved, and how the four phases are delivered can vary widely across programs. An overview of four interdisciplinary programs in the United States is included in Table 4.3, highlighting program setting, specific disciplines used, treatment duration, integration of integrative therapies, billing structure, outcome measures used, payer mixes, and unique features of individual programs. The table helps represent an example of the variability of program structure, components, and payer mixes across successful programs in the United States. The five programs highlight a shared philosophy of

biopsychosocial patient-centered care focusing on education and learning new skills (Table 4.3).[39]

The author will describe below more specifics related to his teams' interdisciplinary program presently provided at the Swedish Health System in Seattle, Washington. This will serve as an example and represent the four phases of interdisciplinary care in more detail. Many of these same principles and treatment philosophies can be applied to the programs in Table 4.3 and interdisciplinary programs in the United States and across the world.

Swedish Pain Services: Functional Restoration Programs Overview

Swedish Pain Services (SPS) is a comprehensive outpatient pain management center in Seattle, Washington, and is part of the Swedish Health System and Providence St. Joseph Health. The functional restoration space, including treatment rooms, gym space, and group rooms, comprises approximately one-third of the clinic's 14,000 square foot facility, including an interventional procedure suite, outpatient clinic space, and support staff offices. SPS offers various outpatient-based interdisciplinary pain rehabilitation programs of various lengths, the most comprehensive being the four week structured functional restoration program (SFRP). The SFRPM program provides care for Medicare, Medicaid, and commercially covered patients referred by primary care and specialty care providers within the healthcare system and externally. The SFRP is a four week, 5 h per day, three day per week program (60 h total). Each program cohort included four patients who received both group and individual treatment with 1 h sessions of physical and OT, RT, and pain psychology. Patients were also seen weekly by a pain medicine specialist, and team conferences were completed every week, where the patient's progress was reviewed, and the rehabilitation team made treatment adjustments. Additional pain education is provided by a nurse pain educator and includes a comprehensive workbook-based and web-based curriculum.

Patients were followed up four weeks after completion of the program and continued to be followed by a pain medicine specialist after discharge. Because of current billing guidance, all disciplines of treatment (PT, OT, pain psychology, RT) are charged on a fee for service basis. Pain education group sessions led by our nurse educator were provided but not a billable service. A less intensive weekly program includes 3-4 h per week of individual and group based PT, OT, pain psychology, and RT. This is offered over a six to eight week period and includes medical visits and scheduled team conferences where patients' progress and adjustments in treatment focus are made by the interdisciplinary team.

Four Phases of Interdisciplinary Care

Comprehensive Interdisciplinary Assessment: The "Comprehensive Evaluation"

Commonly, patients are evaluated by a 2 h "comprehensive evaluation," which includes a 1 h pain psychology assessment followed by a 1 h pain medicine evaluation by a pain medicine specialist. Many programs that treat injured workers may also include a third assessment by a vocational counselor to help assess and guide work related issues, including the return to work and more objective functional capacity assessments. After the individual assessments, the patient's case is discussed in an interdisciplinary manner, and the treatment recommendations are then communicated with the patient. Factors that may preclude a patient from participating in a structured program may include the need to stabilize psychiatric functioning, referral for substance use treatment including opioid detoxification or transition to buprenorphine, or patients' inability to agree with the treatment plan or philosophy, including patients' readiness or willingness to accept a self-management approach. Additional practical barriers may prevent patients from participating, including lack of insurance coverage, excessive out-of-pocket costs, travel restrictions, and inability to take time away from work or other personal responsibilities.

Pre-programming Phase

Prior to starting a structured program, many patients may benefit from short trials in time-limited physical and OT, behavioral health, and RT. These "pre-programing" visits may help to "trial" the program for patients and assess compliance and willingness to comply with treatment philosophy and self-management approach. Trial therapy sessions can include weekly sessions for three to four weeks and include informal team conference discussions with the treating disciplines and the pain specialist where decisions for continuing care are made. This also offers the treating team additional time to work with the patient and familiarize themselves with their individual needs. The pre-programming phase is often necessary for patients with a maladaptive understanding of their pain condition and unstable psychiatric problems that may need to receive more focused behavioral health interventions, including referrals for depression, anxiety, or post-traumatic stress disorder (PTSD). Stabilizing these psychosocial factors will help set up the patient for success in a formal program and ensure a greater likelihood of patient compliance with active and behavioral interventions. Coordination of pre-programming treatments and follow ups was completed with the treating pain medicine physician. The final stage of pre-programming includes a 1 h orientation to the program coordinated by the nurse educator and is done in individual or group format. Patients are given an overview of the program, expectations for care, the importance of individual compliance, and practical questions are answered, including scheduling and parking. The nurse educator can also review the treatment manual and help coordinate how additional online web-based educational materials can be accessed.

Interdisciplinary Care: Formal Treatment Program

Interdisciplinary functional restoration programs combine individual and group based sessions and include physical and OT, behavioral health (i.e. cognitive behavior therapy, mindfulness training), RT, pain education, and aerobic conditioning. The most intense program involves the four week SFRP [60 h of treatment total] and less intense weekly program [18-32 h]. For the SFRP patients, in cohorts of four, they participated in three sessions per week, two session days involved 1:1 therapy sessions and a third session day in groups. Separate from current Covid-19 restrictions, two cohorts or a total of eight patients participated in group sessions. The group setting offers a therapeutic option for patients to learn from each other, provide a sense of validation of their pain, provide an environment to share common concerns, help to increase self-reliance, and be a source of inspiration from other patients in the program.[40] Studies have found that patients participating in groups may help to improve engagement, understanding, share their experiences, and express themselves in a safe and non-threatening atmosphere. The group process can enhance treatment success and patient satisfaction through cognitive

TABLE 4.3 Interdisciplinary Pain Rehabilitation Programs in the United States

Name of Program, System of Care	Mayo Clinic Pain Rehabilitation Center	Pacific Rehabilitation Centers	Savas Health Unitized Transdisciplinary Care™	Stanford University School of Medicine Pain Management Clinic	Swedish Health System, Swedish Pain Services
Location (city, state)	Rochester, MN	Bellevue, Everett, Puyallup, WA	Inland Empire, CA	Redwood City, CA	Seattle, WA
Setting (academic, hospital system, private)	Academic	Private Established CARF Accredited	Private	Academic	Health System
Inpatient/outpatient	Outpatient	Outpatient	Outpatient	Outpatient/Inpatient	Outpatient
Program (s): h/day, days/week, duration	15 day program, weekdays 8 am-4 pm	Six (6) h/day, five (5) days/week, 20 days	The complex pain programs use the Unitized Transdisciplinary Care™ model. One year program consists of: Four cycles: 12 week treatment focusing on specific goals Periods: each cycle consists of three four week periods Units: A Unit is a focused 2.5 h transdisciplinary treatment session combining group and individual treatments. The frequency of Units depends on the participant's conditions, goals, and progress and is adjusted throughout the program.	Various programs including: Outpatient: Pain psychology services/therapy, with or without biofeedback (weekly for four to eight sessions); Free CBT Pain Coping Skills Group (2 h, once a week for eight weeks); CBT + Movement Group (pain psychology + PT [Tai Chi] [3 h, once a week for eight weeks]); Back in Action (pain psychology, MD + physical therapy): 4 h twice a week for six weeks; All About Sleep and Pain Group (pain psychology + sleep psychology): 2.5 h once a week for six weeks; Pain and Purpose (ACT based group): 2 h once a week for six weeks); Empowered Relief (2 h, one time PNE intervention); Inpatient: Stanford Comprehensive Interdisciplinary Pain Program (SCIPP): inpatient stay varies based on patient needs.	Two programs: 1. Structured Functional Restoration Program (SFRP): 5 h/day, three days per week for four weeks; two days 1:1, one day group sessions. Round-robin 1 h PT, OT, relaxation training, pain psychology, and nursing education lecture. Weekly pain medicine visits Weekly team conference meetings 2. Weekly Functional Restoration Program (1:1): 4 h per day, six to eight weeks, 1 h round-robin of PT, OT, pain psychology, and relaxation training, with additional 1 h pain education lecture. Group pain psychology class weekly by virtual visit.

Continued

TABLE 4.3 Interdisciplinary Pain Rehabilitation Programs in the United States—cont'd

Name of Program, System of Care	Mayo Clinic Pain Rehabilitation Center	Pacific Rehabilitation Centers	Savas Health Unitized Transdisciplinary Care™	Stanford University School of Medicine Pain Management Clinic	Swedish Health System, Swedish Pain Services
Disciplines (PT, OT, Pain Psych, Relaxation training, Vocational counseling) If groups, #/group, or cohort	Psychiatry, psychology, NP, OT, RN (case managers), PT, Vocational counseling, biofeedback training Group based practice with a rolling admission model. Approximately 25–27 patients were actively receiving care at any point in time.	Medicine (PM&R) & Nursing Psychology (Licensed) & Relaxation Vocational Counseling Physical Therapy Occupational Therapy 10–12 Patients/group/ clinic	The transdisciplinary concept establishes the participant's needs and combines the services that each treatment team member can perform based on their training, experience, and certifications. The transdisciplinary team consists of: Medical: Medicine MD (Anesthesia, PM&R), Physician Assistant, Nurse Practitioner, Care Manager (RN), and Care Coordinator (LVN); Behavioral Health: Pain Psychology (Licensed), LMFT, LCSW; Physical Reconditioning: Chiropractic, Massage, Physical Therapy, Mindful Movement Classes (combines elements of Yoga, Tai Chi, Feldenkrais); Alternative Therapies: Acupuncture, Chinese Medicine, Naturopathic Medicine, Dietitian) --- Eight to 12 Participants/ Unit	Medicine MD (Anesthesia, Neurology, Dentist), Physician Assistant, Nurses, and Nurse Practitioner Pain Psychology (Licensed) and Pain Psychology Fellows (two to three Fellows/year), Pain Physicians and Fellows, Complex Case Care Managers, Physical Therapy Acupuncture, eight to 12 patients/group	Medical: Pain Medicine Specialist (PM&R/Anesthesia) Behavioral Health: Relaxation Training (certified) Pain Psychology (PhD) Nurse Educator (RN, PhD) Physical Therapy (DPT): (traditional PT training, pelvic PT, and Pain Neuroscience Education [PNE]) Occupational Therapy (OT): (traditional OT training & Tai Chi) Structured Functional Restoration Program: cohorts of four patients, per group, two to three groups per month. Weekly Functional Restoration Program (six to eight weeks). Six to eight patients/cohort
Behavioral Health Interventions	CBT, mindfulness, ACT (disproportionately CBT-based)	Individual and Group CBT	CBT, Mindfulness, Motivational Interviewing, Meditation	CBT, Mindfulness, ACT, Biofeedback, Hypnosis, Motivational Interviewing	CBT, Mindfulness, ACT, Motivational Interviewing, Relaxation Training, Biofeedback
Integrative therapies: yoga, Tai Chi, acupuncture	Yoga, Tai Chi	Yoga, Tai Chi	Tai Chi, yoga, acupuncture	Tai Chi, yoga, acupuncture	Tai Chi, Qigong
Virtual Services (yes/no)	Yes	Yes - Full CARF Accredited IPR Program Track via Secure Telehealth (patients' homes)	Yes	Yes	Yes
Billing: fee for service, day rate, case rate	Fee for Service	Daily Rate	Case Rate	Fee for service, Empowered Relief, Pain Science Lecture Series, CBT follow up group, and eight week CBT Pain coping skills offered free of charge	Fee for service
Payers: workers compensation, commercial, Medicare, Medicaid	Commercial, Medicare, WC	Workers' Compensation (Labor and Industries & Self-Insured Employers)	Medicaid	Commercial, Medicare, Worker's Compensation	Commercial, Medicare, Medicaid, self-insured. No WA State workers compensation coverage, patients referred to local SIMP accredited programs.

TABLE 4.3 Interdisciplinary Pain Rehabilitation Programs in the United States—cont'd

Name of Program, System of Care	Mayo Clinic Pain Rehabilitation Center	Pacific Rehabilitation Centers	Savas Health Unitized Transdisciplinary Care™	Stanford University School of Medicine Pain Management Clinic	Swedish Health System, Swedish Pain Services
Outcome Measures: PHQ-9, GAD-7, PCS, ODI, 6 min walk test, PEG	Self-report - WHYMPI (pain severity and pain interference scales only), SF-36, PHQ-9, PCS, PSEQ, PCL-5 Performance based measures (administered by physical therapy) - Simmonds Physical Performance Test Battery. Battery includes: 5 min walk, 50 foot walk, timed up-and-go, repeated sit to stand, repeated trunk flexion, loaded reach Occupational Therapy - Canadian Occupational Performance Measure (COMP)	PHQ-9, GAD-7, PCS, ODI, TKS, WHODAS-2, Mid-Range Lift, Chair to Stand Test (CST)	PROMIS NPRS PEG ODQ PDI PHQ-9 GAD-7 PCS PGIC DAST-10 AUDIT	CHOIR (including PROMIS) PCS CES-D PCL CPAQ-8 PASS-40 PSEQ TSK	BESS Balance Test CPAQ-8 COPM GAD-7 ODI PEG PHQ-9 PCS PSFS TSK Five times sit to stand test 6 min walk test
Level of Medical Management: opioid detoxification, medication trials,	Opioid detoxification was concurrent with programming. Additional tapering of benzodiazepines, muscle relaxants, hypnotics when appropriate	Medication trials (non-opioids), opioid tapering and elimination, coordination with inpatient detoxification, and substance abuse treatment programs. Individual/group patient education	Medication trials (non-opioids), opioid tapering, Medication Assisted Treatment integrated into the program (MAT-Units)	Medication trials (non-opioids), opioid tapering and optimization EMPOWER, inpatient comprehensive interdisciplinary pain program (SCIPP), transcranial magnetic stimulation study, Pain Science Lecture Series, Individual/group patient education	Medication trials (non-opioids), opioid tapering, and optimization.Board certified addiction specialist integrated into clinical practice and available for consultation, coordination of care for medication management (buprenorphine), and tapering
Aftercare, maintenance services, classes	Monthly, in-person aftercare program (one day group)	Follow Up Community Reintegration (4 h/day, two days/week, three weeks) In Clinic and Virtual Tracks	Follow up available at pain clinics under the FFS model with incorporated community services	Maintenance services, free monthly CBT/ACT follow up classes	Maintenance group classes for PT, OT, relaxation training, pain psychology

Continued

TABLE 4.3 Interdisciplinary Pain Rehabilitation Programs in the United States—cont'd

Name of Program, System of Care	Mayo Clinic Pain Rehabilitation Center	Pacific Rehabilitation Centers	Savas Health Unitized Transdisciplinary Care™	Stanford University School of Medicine Pain Management Clinic	Swedish Health System, Swedish Pain Services
Unique features:		Only full service interdisciplinary telehealth CARF program in the region	– Scalable transdisciplinary solution based on a proprietary software platform – Use of proprietary assessment system to allow for easy communication among disciplines and goal tracking (Patient Global Health Score™) – Use of artificial intelligence driven predictive modeling for optimal treatment planning and execution – Regular Systematic Case Review by the treatment team for all participants	Pain Psychology and MD Fellowship programs, only med-behavioral inpatient pain experience in the western United States (SCIPP), Bi-weekly interdisciplinary case conference	Pain rehabilitation programs integrated within physical space and cost center of comprehensive pain center hub for the large health system. Behavioral health co-treatment with integrated behavioral health services in the system's primary care clinics helps stabilize patients prior to and provide additional behavioral health support after completing structured programs.
Program Content Contributors	Wesley Gilliam, PhD	Michael D. Harris, PhD	Tobias Moeller-Bertram, MD	Kristen Slater, PhD Heather Poupore-King, PhD	Becca Taylor, RN, PhD Wilson Chang, MD

AUDIT, Alcohol Use Disorders Identification Test;
BESS, Balance Error Scoring System;
CES-D, Center for Epidemiological Studies Depression;
COPM, Canadian Occupational Performance Measure;
CPAQ-8, Chronic Pain Acceptance Questionnaire-8;
CHOIR, Collaborative Health Outcomes Information Registry;
DAST-10, Drug Abuse Screening Test-10;
GAD-7, Generalized Anxiety Disorder-7;
NPRS, Numeric Pain Rating Scale;
ODI, Oswestry Disability Index;
ODQ, Oswestry Low Back Pain Disability Questionnaire;
PASS-40, Pain Anxiety Symptoms Scale-40;
PCL-5, PTSK Checklist for DSM 5;
PCS, Pain Catastrophizing Scale;
PEG, Pain, Enjoyment in Life and General Activity [PEG] Scale;
PDI, Pain Disability Index;
PHQ-9, Patient Health Questionnaire-9;
PGIC, Patient Global Impression of Change;
PROMIS, Patient-Reported Outcomes Measurement Information System;
PSEQ, Pain Self-Efficacy Questionnaire;
PSFS, Patient Specific Functional Scale;
SF-36, Short Form Survey- 36 Item;
TSK, Tampa Scale of Kinesiophobia;
WHODAS-2, WHO Disability Assessment Schedule 2.0;

behavior interventions applied by all members of the treatment team.[41]

The program was led by a pain medicine specialist (physiatrist or anesthesiology pain medicine specialist) along with a nurse educator, who helps to coordinate the patients' treatment program, guide progress, and provide any needed interventional therapy, medication management, or ongoing explanation of the complex nature of the patients' pain. Patients are seen for medical follow up visits every week and at scheduled visits after completion of the program. The emphasis during medical visits is on assessing progress in the program, reviewing patient compliance across disciplines, sharing feedback from the treating team on patient progress, and any change in treatment recommendations. The structured environment provides an opportunity for time-limited medication trials, including opioid tapering and detoxification, analgesic and adjuvant medication adjustment, and medication regimen simplification.[42,43] Pharmacotherapy commonly focuses on analgesia, mood, and sleep.

Most importantly, the pain medicine specialist role focuses on understanding the complexities of the patients' past treatments, diagnostic workup, related psychosocial and vocational factors, and clarifying and educating about the treatment diagnoses. During and after formal participation, the pain medicine specialist helps to motivate the patient to integrate techniques and skills learned in the treatment program across all disciplines (Table 4.4)

The following short summary highlights the skills and techniques used in interdisciplinary care for PT and OT, behavioral health, and RT, many times more specialized than more unimodal therapy approaches. Many patients may also present with "yellow flags" traditionally thought to be unhelpful beliefs, avoidance of activities, and psychologic factors of distress that are risk factors for long term distress and disability. Common yellow flags include psychological factors such as fear avoidance behavior, catastrophizing, depression, and heightened anxiety.[44] Their initial assessment needs to lay the foundation for a positive-clinician-patient therapeutic alliance that can foster a sense of collaboration, understanding, and support between the patient and team member.[45]

Physical Therapy

Physical therapy (PT) recommendations for exercise may be challenging for patients undergoing interdisciplinary treatment. Many patients have poor prior experiences with active PT in the past and may not have remained compliant with previous PT recommendations and exercises because of increases in pain. In addition to integrating techniques from other disciplines while participating in interdisciplinary-based PT (such as meditation, diaphragmatic breathing, mindfulness, and pacing concepts), several key points concerning an exercise prescription of chronic pain include reassuring patients that it is safe to move, exercise should be time, as opposed to pain contingent, using a tolerable or intolerable dichotomy. In addition, the physical therapist helps patients develop a comprehensive home program that also includes flare up exercise plans, the importance of self-monitoring exercise, and an emphasis on developing and retaining movement confidence and quality (Table 4.5).[46]

PT involves an initial comprehensive assessment based on a diagnostic classification system. Therapy combines manual therapy, strengthening, and joint stabilization exercises, and an additional emphasis on the nervous system and pain education based on clinical practice guidelines.[47,48] The Swedish Health System program has integrated staff certified and trained in chronic pain education based on evidence-based work by physical therapists Lorimer Mosely, David Butler, and Adrianne Louw, Pain Neuroscience Education (PNE). PNE includes an understanding by the therapists (and treatment team) of contemporary pain biology concepts that help patients better engage in a meaningful and constructive dialog as the "explain pain" to patients.[49]

PNE de-emphasizes pathoanatomic educational content focusing on teaching patients about the complex neurologic, psychological, and physical contributors to the development of pain. Some examples of content within a PNE program may include the purpose of pain (i.e. pain as an alarm system warning of actual or potential tissue damage, pain's influence on thoughts, emotions, actions, and activities), peripheral nerves (i.e. signal transmission including synapses and neurotransmitters, ability to modify the excitability of peripheral nerves), the central nervous system (i.e.

TABLE 4.4 Pain Medicine Physician's Role on the Interdisciplinary Team: Goals and Responsibilities

- Clarify the diagnoses, explain the roles and goals of treatment team members
- Educate and explain treatment philosophy
- Pharmacotherapy focusing on analgesia, mood, and sleep
- Simplify medication regimen, guide tapering of opioids when appropriate
- Put the patient's reported history or "story" together and shift their focus to the present and learn new skills
- Prioritize and help patients establish realistic goals, set the context for success
- Help engage patient to change and embrace a biopsychosocial model
- Be flexible, use motivational interviewing techniques
- Guide, encourage, give feedback on progress, and review team conference notes
- Provide conflict resolution between patient and team members
- Celebrate successes and help patients to manage setbacks
- Reassess the need for additional diagnostic workup, referrals to other specialists and therapists before, during, and after formal interdisciplinary treatment

TABLE 4.5 Key Points About Exercise Prescription for Chronic Pain

- Understanding contemporary pain biology and "explaining pain" are key competencies required for biopsychosocial treatment
- Frequently reassure patients it is safe to move/pace despite their symptoms
- Exercise prescription should be time, as opposed to pain, contingent on a tolerable/not tolerable dichotomy
- Have ready-made responses to flare-ups can reduce the severity
- Exercises should be individualized, enjoyable, related to patient goals, and with a level of supervision specific to the patient
- Many patients with chronic pain will respond to a lower exercise dosage than recommended for healthy individuals (i.e. graded low to moderate intensity)
- Closely observe and monitor exercise practice, seek and provide feedback, and correct poor technique
- Encourage patients to self-monitor exercises (diaries, activity trackers)
- Emphasize developing/restoring movement confidence and quality

Booth J, Moseley GL, 2017.[46]

the brain's role in the production of pain and the influence of beliefs, emotions, and attention on pain production), chronic pain (i.e. dissociation between pain and tissue damage, and the maladaptive nature of chronic pain), and treatment strategies (i.e. benefits of pain knowledge, stress relief, sleep hygiene, graded exercise, and activity).[50]

Over the four week program, a patient-centered home exercise program was developed based on patient needs and clinical areas of focus. The "home program" includes aerobic conditioning (daily walking, treadmill), joint and core muscle stabilization, neurodynamic training, stretching, and instruction on manual muscle self-release. Techniques and strategies from other disciplines (i.e. pacing, deep breathing, mindfulness) and concepts of PNE and graded exercise dosing are integrated into how a patient will self-progress and self-modify their PT regimen daily (Table 4.6).

Occupational Therapy

Occupational therapy (OT) focuses on posture assessment and training, pacing, and goal setting to improve instrumental activities of daily living (IADLs), including homemaking, yard work, shopping, driving, sleeping, hobbies, and traditional joint protection and compensatory strategy training. Initial assessment includes COMM and completion of daily activity "time pies," providing a visual report of how patients spend the day on an hourly basis, including self-care, work, family, friends, work, housework, and leisure/recreational activities. Over the four week SFRP program, patients complete their own self-management activities "tool box" that includes pacing, setting realistic daily goals, work simplification, prioritizing, and delegating as needed.

Pacing

A central component of OT in the SFRP program and many interdisciplinary programs is the concept of pacing, a skill that is often overlooked in traditional biomedically based pain treatment. "Activity pacing" may be considered part of time management training to find a balance between overdoing and underdoing activities built around a patient's own more structured daily schedule. Activity pacing is used clinically to describe behavioral strategies taught or encouraged to help patients, in the context of pain management, to better cope and function with chronic pain.[51] Pacing includes determining the amount of activity that can be done without causing a pain flare up. It allows one to be more productive, conserve energy for doing goal-oriented activities, and better manage their pain (Table 4.7).

Fordyce classically identified two types of maladaptive activity pacing patients: (1): recliners, "recliners," who tend to rest when pain increases and are more likely to rest in response to pain, and (2): "pacers," whom Fordyce described as those who "paced" or walked back and forth unable to decrease or stop activity.[3] In this example, Fordyce's "pacer" or walked back and forth unable to decrease or stop activity. The more recent use of the term "pace" or "pacer" is a positive and more adaptive use of the term. Interestingly, both maladaptive patterns (recliners and pacers) can be problematic and lead to more pain and more pain flare-ups. The "recliner" may become more deconditioned and weaker and, when faced with an increase in activity, may experience increased pain. The "pacer" may overdo an activity and experience a subsequent delay in the aversive effects of over-activity, making it difficult to appreciate any connection between over-activity and subsequent pain. Fordyce's approach focused on gradually increasing activity with behavioral strategies where positive reinforcement of activity becomes time-contingent or goal-contingent in distinction from pain contingent. Keefe et al. expanded on Fordyce's quota-based interventions with interventions focused on activity management or "appropriate pacing," where patients not only focus on goal-related activities, like increasing walking distance or sitting and standing tolerances but also increasing general activity throughout the day by a percentage of a safe "baseline" in a systematic manner with the use of activity-rest cycling. This approach includes the use of activity diaries.[52,53] The SFRP OT curriculum focuses on these concepts. It helps patients individually assess and understand how to apply these skills and strategies to understand that activity pacing is "a regulation of activity level and/or rate in the service of an adaptive goal or goals" based on an updated definition of activity pacing. Many patients may continue to struggle to apply the pacing technique after formal treatment and like other skills learned in an interdisciplinary program, follow up, and reassessment, re-encouragement of applying techniques remains an important aspect of ongoing follow up to maintain patient engagement.[54]

TABLE 4.6 PT Exercise Evolution With Pain Education Techniques

Progress Over Time	Modify When Pain Is High
Start with two sets, build to three	Decrease number of sets
Build more repetitions (>ten repetitions) to increase endurance	Add rests between each repetition
Improve coordination and control	Decrease range of movement to within comfort
Improve body awareness and sensation connection	Decrease the total time in activity
Add weight or resistance if necessary or possible	Use relaxation breathing to support movement and breathe between sets while resting
	Practice imagery of movement with no pain while resting

Swedish Pain Services, Structured Functional Restoration Program. Tim Zepelak, DPT, 2020.

TABLE 4.7 Swedish Pain Services Functional Restoration Program: OT Pacing

1. Deciding on reasonable activity goals based on what you value.
2. Establish time baselines of your present time limits and tolerances for activities on both a "good" day and a "bad" day to determine a present baseline.
3. Gradually increase the time spent doing a task.
4. Planning your daily activity level on pre-set realistic goals.
5. Prioritizing, organizing, and breaking up your daily activities.
6. Delegating less important tasks to others.
7. Breaking activities up into smaller tasks or parts.
8. Taking rest breaks between tasks.
9. Working at a slower, less intense pace.
10. Breaking up high and low intensity tasks during the day or over the week.
11. Use the best hours of your days for the most demanding task.
12. Vary or change tasks often, so you use different parts of the body.

Additional clinical focus within OT individual and group sessions includes educating and training in movement therapies. Movement therapy includes a range of Eastern and Western mindful-based practices that helps to promote a patient-centered proactive participation in one's health by innately promoting health and wellness and commonly include the practice of Tai Chi, Qigong, Yoga, Pilates, and the Feldenkrais Method.[55] The SFRP program focuses primarily on teaching Tai Chi, which has strong evidence for improving pain and mood in several chronic diseases, including chronic pain.[56] Tai Chi is based on an ancient Chinese system of meditative movement that has evolved to provide low-impact exercises, joint mobilization, and improve body awareness, balance, and posture.[57] Tai Chi includes a series of movements or "forms" that can be practiced from 5 to 20 min per session (Table 4.8).

Compliance and integration into patients' daily routines with Tai Chi, as well as other movement-based therapies, has significantly improved with the more recent ability to provide web-based videos, program content on video link platforms (i.e. YouTube), and the increase in community availability for patients to continue with movement-based therapies at local gyms and exercise facilities.[58]

Pain Psychology

Many chronic pain patients present with varying levels of psychosocial distress, such as depression and anxiety, elevated catastrophic thinking, maladaptive ideas about their pain condition, and previous or active physical or psychological trauma. Pain psychology emphasizes CBT, mindfulness training, and acceptance and commitment therapy provided in individual and group therapies.[59,60,61] The reader is directed to Chapter 58 on behavioral interventions for pain.

All patients were evaluated by a treating pain psychologist prior to starting the structured program. Patients are often scheduled for a "comprehensive evaluation," a 2 h assessment, where the patient is first evaluated by the pain psychologist followed by the pain management specialist. Patient specific needs, including the need for stabilization or initiation of related psychological therapies, are assessed at the evaluation and may include referral for psychiatric and psychological counseling, treatment of substance use disorder, or treatment for more specific disorders such as PTSD offered within the hospital system, external community private practices, or community mental health clinics.

Behavioral health interventions at SPS include mindfulness-based cognitive therapy that helps to address pain amplification and maintenance provided over the four week program, including eight individual and four group sessions.[62] MBSR has been shown to be an effective intervention for several medical conditions, psychological disorders, chronic pain, improving pain, and reducing psychological distress.[63] Mindfulness-based CBT includes sessions addressing automatic pain habits, facing the challenge of chronic pain, using the breath as an anchor, staying present, acceptance, understanding thoughts, taking care of myself, and harnessing the power of the mind (Table 4.9).

Besides a focus on cognitive behavioral factors such as depression, anxiety, catastrophizing, and pain coping, the mindfulness-based cognitive therapy training addresses extreme thinking, selective attention (overgeneralization, filtering, disqualifying the positive, magnification/minimization), relying on intuition (emotional reasoning, mind reading), and blaming (personalization, labeling and mislabeling), and helps patient practice mindful movement and other "mindful" exercises, teaching patients to be present in the sensations of one's body, pleasant experiences diary taking, using the breath as an anchor, and meditation. Additional group lectures include education and discussion of the gate control theory of pain, pain neuromatrix, stress-pain connection, and sleep.

TABLE 4.8 Key Characteristics of Tai Chi

Tai Chi Characteristics	Brief Description
Circular	All movements flow in a circular path, promoting dynamic stretching and balance
Relax	Deep breathing facilitates relaxation throughout the entirety of the practice. Overexertion is avoided
Calm	Calmness in movement and mind, meaning no excessive movements and the mind is clear of superfluous thoughts
Continuous	Smooth transitions with one movement flowing to the next
Intent	Mind is present and fully focused on moving with purpose
Energy	Movements are biomechanically efficient, using the least amount of effort to execute

Phuphanich ME, Droessler J, Altman L, Eapen BC. Movement-based therapies for rehabilitation. *Phys Med Rehabil Clin N Am.* 2020;31:577-591. doi:10.1016/j.pmr.2020.07.002.[57]

Relaxation Training

Relaxation therapy (RT) uses evidence-based techniques to help patients release or reduce mental, emotional, and physiologic tension. Studies have shown the benefits of relaxation and biofeedback in several medical conditions, including pain conditions such as low back pain, headache, and chronic musculoskeletal pain.[64,65,66] The goals of relaxation therapy at SPS include learning nervous system balancing techniques, maintaining a physiologic balance, increasing a sense of calm, and decreasing overall tension. The "relaxation response" was defined by Benson et al. in the 1970s as a physiologic and homeostatic state that counteracts stress.[67] Relaxation response can be achieved by several techniques, including visualization, muscle relaxation, massage, breathing techniques, meditation, and mind body exercises such as yoga and Tai Chi. Teaching patients various techniques to induce a relaxation response is a key focus of RT.

Formal biofeedback training includes measuring various physiologic responses such as auditory, visual, or tactile feedback about physiologic processes from the autonomic nervous system, including muscle tension, heart rate, and skin conductance. Patients learn to self-regulate their physiologic processes with the help of "feedback" of their physiologic functioning that is provided while in session with the relaxation therapist, often inducing or facilitating a relaxation response. Feedback may include surface EMG-measured muscle tension, skin temperature, heart rate variability, or respiratory biofeedback.[68]

Patients are taught basic concepts of nervous system physiology, including unique features of the parasympathetic (calms

TABLE 4.9 Mindfulness-Based Cognitive Behavior Therapy (CBT)

	Mindfulness-Based CBT Sessions	Clinical Context and Example
1	Stepping out of Automatic Pain Habits	Pain can seem unpredictable to many patients. Helping them identify habitual behaviors contributing to the pain-stress cycle is an important first step for treating pain
2	Facing the Challenge	Managing pain is stressful, and reacting to stress can be a powerful habit. Mindfulness meditation can help patients learn to respond rather than react to stress
3	The Breath as an Anchor	Stress, pain-related or not, may stem from dwelling on the past or the future. Learning how to ground oneself using one's breath is the best way to connect to the present moment, which can reduce stress
4	Learning to Stay Present	Pain- and stress-related self-talks can occur without awareness. Improving awareness allows patients to choose how to respond to unhelpful self-talks
5	Active Acceptance	Many patients have a hard time accepting pain, which leads to poor self-management. Breathing with pain during meditation promotes acceptance and reduces pain-related stress
6	Seeing Thoughts as Just Thoughts	Buying into unhelpful, habitual self-talks may lead to the same disappointing results for pain management. Learning how to pause, become aware, and respond is the key to obtain a different result
7	Taking Care of Myself	Struggling with pain management may indicate a lack of self-care. Practicing key elements of mindfulness meditation—awareness, acceptance, and compassion—may promote better self-care
8	Harnessing the Power of Mind for Chronic Pain Management	Sitting with strong sensation, thoughts, and emotion can be challenging, regardless of how long one has been practicing mindfulness meditation. Session eight draws on the body scan meditation and 3 min breathing space meditation, two foundational practices, to promote mind body awareness and to help patients reflect on progress made during the program

Adapted from Melissa Day, Ph.D. "Mindfulness-based cognitive therapy for chronic pain: a clinical manual and guide" (Ref. 64), and Sharon Hsu, PhD, Swedish Pain Services, Seattle, WA.

the body to conserve and maintain energy) and sympathetic (i.e. arouses body to expend energy) nervous system.[69,70]

Additional training context is provided with a focus on vagus nerve action and physiology, the primary driving force of parasympathetic tone, as an important regulator of stress, anxiety, and anger.[71] This helps to explain to patients the physiology behind creating a relaxation response. Patients are also introduced to the concept of the "fight or flight" stress response, including various unhelpful consequences that develop with chronic or persistent pain. The four primary relaxation tools taught include diaphragmatic breathing, progressive and passive muscle relaxation, autogenic training, and guided imagery (see Table 4.10: RT techniques). Patients are encouraged to integrate RT with other skills taught in other disciplines, such as Tai Chi in OT, during exercises or stretches in PT, and mindfulness training with pain psychology. Over the four week treatment program, emphasis was placed on integrating relaxation at home, work, during their daily routine, and during flare-ups. Patients are also given resources to continue their daily integration of RT, including personal recorded sessions on their smartphone or iPads, various breathing training apps (Breathe2Relax; Breath+), and relaxation therapy videos provided via links to our hospital YouTube site and other commercial platforms.

Nursing Education

A full-time nurse educator helps to coordinate all aspects of patient care from the initial assessment, pre-programming, during formal interdisciplinary care, and post-treatment. The nurse educator's role as a nurse navigator helps to provide ongoing and consistent messaging around program goals and procedures. The nurse educator also provided educational support and additional RT for patients. Lectures provided in group sessions of four to eight patients included topics such as orientation to self-management programs, sleep, nutrition, medication pharmacology, and side effects (Table 4.11).

Post-program: Follow Up Care, Outcome Assessments, and Maintenance Classes

Four weeks after completing the four week SFRP program, patients were re-evaluated by the pain rehabilitation team, which included 30 min round-robin like scheduled visits with their treating PT, OT, pain psychologist, relaxation therapist, and pain medicine specialist. Progress and compliance across all disciplines were re-assessed, and home programs were adjusted. Medical follow up helps assess core outcomes related to pain, pain flare-ups, mood, and sleep quality. Patients may be referred back to their referral provider or continue medical management with a program pain medicine specialist. Additional "maintenance" aftercare classes are provided to patients and are usually delivered in a group format monthly or quarterly. Time-limited follow ups with PT, OT, psychology, and relaxation are also provided for patients who need upgrades in their current self-management program and are coordinated by their managing pain medicine specialist. The integration of virtual health into the functional restoration program has included pain psychology and pain medicine virtual visits, pain psychology virtual individual and group visits. As a hospital-based outpatient clinic, our center cannot provide physical and OT through our virtual platform.

Outcome measures tracked pre-program at time of comprehensive evaluation, after the treatment program, and at the four week follow up team visit. Assessments and questionnaires include the average pain, enjoyment in life, and general activity (PEG),[72]

TABLE 4.10 Relaxation Training Techniques

Exercise	Technique (example)
Diaphragmatic breathing (DB)	Breathe through your nose (inhale) while pushing abdomen out; breathe out (exhale) while pushing abdomen in
Progressive muscle relaxation (PMR)	Tense and release muscle groups, distally to proximally; hands (clench); wrists and forearms (extend and bend hands back); shoulders (shrug toward ears); cheeks and jaws (smile as widely as you can); hips and buttocks (press buttocks together tightly). Hold tension for 4-10 s, then release and relax for 15-30 s
Grounding exercises	"5-4-3-2-1"; five things you see, four things you feel, three things you hear, two things you smell, and one thing you taste
Autogenic training (AT)	Six step sequence allows patients to observe sensations in the body passively. Examples: limbs feel heavy, limbs feel warm, breathing is comfortable, abdomen feels warm, forehead feels cool, and heart is beating calmly or regularly
Guided Imagery	Guided experience encourages mentally generated images that simulate or re-create the sensory perceptions: sight, sound, taste, smells, and touch

Swedish Pain Services: Structured Functional Restoration Program Patient Program Resources, Katie Kapugi, Relaxation Therapist, 2020.

disability (ODI),[73] affective distress (depression [PHQ-9],[74] anxiety [GAD-7],[75] activity engagement [Chronic Pain Acceptance Questionnaire (CPAQ]),[76] catastrophizing (Pain Catastrophizing Scale [PCS]),[77] fear of movement (Tampa Scale for Kinesiophobia [TSK]),[78] and physical activity tolerance (6 min walk test).[79]

Patient Challenges: Need for a Team Approach and Stakeholder Coordination

Practical challenges to providing this type of service despite the powerful clinical outcomes include significant out-of-pocket expenses for many patients, limitation of coverage for multiple group sessions, multiple co-pays, and poor reimbursement even for those "covered" services. In many cases, "pain rehabilitation" programs were not considered covered services under their respective plans and/or behavioral health, and RT coverage is limited or covered by a third party insurer. Many patients could not participate in the treatment program because of similar out-of-pocket expenses and coverage issues.

Central to the success of interdisciplinary care is the importance of a well-functioning team and ongoing communication between caregivers, usually structured within weekly team conferences.[80]

TABLE 4.11 Topics: Pain Education Classes (See Table 4.11)

Pain Education: Class Curriculum	Group Session (four to eight patients): Led by Nurse Educator
PROGRAM ORIENTATION – Prior to the program: Virtual & in-person orientation – First day: Rules of the program, expectations – Preparing your own "Pain Toolbox"	NUTRITION – Anti-inflammatory diet – Pain triggers in your diet – Healthy eating habits
SLEEP AND CHRONIC PAIN – How is sleep regulated? – Co-occurring conditions: insomnia, sleep apnea, mood disorders, PTSD – Sleep Hygiene: Habits for sleeping better	MEDICATIONS FOR CHRONIC PAIN – Managing your medications effectively (how to track, one pharmacy, safe storage, communication with Doc) – Over the counter medications (ASA, NSAIDs) – Anti-depressants, Anti-convulsants – Opioid Therapy: dependency, tolerance, addiction, tapering, benefits, harms – Benzodiazepines & Muscle Relaxers

*Swedish Pain Services, Seattle, WA. Structured functional restoration program patient workbook (Becca Taylor, RN).

Attributes of a well-functioning team include members of the treatment team working in a collaborative, integrative environment, with open communication, and the ability for consensus building and resolution of any conflict relating to a patient's treatment program

Patients may be resistant to taking a more active role in self-management after many failed interventions, ongoing impact, and chronic pain. Readiness for change and accepting a biopsychosocial philosophy is an early challenge for patients starting a program. Early in the program, besides learning many different and new skills, a focus includes increasing compliance with practicing techniques (i.e. diaphragmatic breathing, stabilization exercises, Tai Chi), applying skills (i.e. pacing, setting limits), and "unlearning" maladaptive thoughts or ideas about their pain. Ongoing dialog between the patient and the pain management specialist and individual therapists is an important part of the journey patients take part in the course of treatment. Consistent messaging and the openness to reassess and modify short and long term treatment goals are critical to the success of patients benefiting from the program and maintaining and applying skills, being compliant with "their program" after discharge from formal treatment.

The common core components of CBT described by McCracken and Turk, and Hatchell and Mayer can be shared and reinforced by the entire interdisciplinary team and include promotion of self-management approach, relaxation skills training, cognitive restructuring, behavioral activation (goal setting and pacing), problem solving, skills training, habit reversal (i.e. identifying and unlearning maladaptive ideas and behaviors), and maintenance and relapse prevention.[81]

Outcomes for Interdisciplinary Care

Multiple studies, including systematic reviews and meta-analyses, have demonstrated the efficacy of interdisciplinary treatment programs for many chronic pain conditions, including

low back pain, fibromyalgia, musculoskeletal pain, and chronic headaches.[82,83,84] Chou et al. reviewed the evidence for non-pharmacologic therapies for chronic low back pain, finding evidence for interdisciplinary care along with CBT and spinal manipulation were moderately effective.[85] A systematic review of multidisciplinary rehabilitation programs, which included less intense interdisciplinary treatment programs, examined randomized placebo-controlled studies of any intensity that included a physical component and one or both of a psychological component or social work, finding multi-disciplinary more effective than usual care (moderate quality evidence) and physical treatments (low quality evidence) in decreasing pain and disability.

A recent large-scale study of interdisciplinary pain treatment programs found short and long term effect sizes but moderate long term effect sizes for pain, pain interference, and perceived health. In this study, patients with higher levels of perceived disability and suffering showed greater treatment improvement,[86] while other studies have demonstrated improvements in pain, mood (depression and anxiety), medication usage, activity level, and return to work.[87,88]

Murphy et al. examined outcomes across six interdisciplinary pain programs across the Veterans Affairs system (Albuquerque, Cleveland, Puget Sound, San Francisco, Tampa inpatient, Tampa outpatient). The diverse group of programs primarily included group based treatments, with some offering individual psychotherapy, goal setting, and medical visits.[89] Program intensity, disciplines offered, and scope from daily to two/three days per week, 3–6 h per session, and 5–12 weeks. One program site offered both outpatient and inpatient programs, the latter incorporating opioid detoxification and services for veterans from out of state.[89] Overall, all programs demonstrated significant improvements from pre-treatment to post-treatment in nearly all outcomes (consistently with all programs for pain-related functioning, reduced sleep difficulties, and pain catastrophizing). Many programs have demonstrated improved vitality, negative affect, and reduced pain. Effect sizes ranged from medium to large and were positive despite differences in structure, duration of treatment, and resources.

Interdisciplinary Care: A Place for Reduction or Tapering of Opioids

Murphy et al. also examined veterans participating in a three week inpatient interdisciplinary pain program comparing subjects using opioids and agreeing to an opioid taper (average morphine equivalent of 61 mg/day) compared to subjects not receiving opioids for primarily low back, neck, and extremity pain.[90] Individuals in both groups experienced significant improvement in all areas of treatment, including pain reduction, ADLs, mobility, negative affect, pain-related fear, pain-symptom amplification, coping skills, catastrophizing, and sleep. Gradually tapering opioids while participating in an interdisciplinary program, even for those who perceived opioids as beneficial, did not negatively impact treatment outcomes.[90]

Gilliam et al. reported outcomes for a three week interdisciplinary pain program with a supervised opioid taper (average MME = 40) compared to non-opioid users. At discharge and at six months, irrespective of opioid use status, both groups demonstrated improvements in pain, mood, and physical function.[91] In a similar tertiary based interdisciplinary program, high dose opioid patients weaned from opioids showed improvements in pain, depression, anxiety, and pain-related function versus lower dose or no opioids. Seventy three percent of weaned patients remained off opioids, and although treatment benefits declined at six and 12 months after completion, benefits remained clinically significant.[92] A recent study of functional MRI imaging changes following interdisciplinary treatment showed significant improvements in standard outcomes measures, increases in total brain volume, and changes in more specific brain volume that correlated with patient perception of change. Differential program effects were found between opioid and non-opioid use in patients with changes in specific brain areas.[93]

Economic Analysis of Interdisciplinary Treatment

Sletten et al. analyzed the economic outcomes of a three week, five day per week, daily SFRP and found a significant reduction in medical costs between 64% and 90% from three to 18 months post-treatment.[94] Proctor et al.'s prospective study of 1440 patients with chronic work related musculoskeletal disorders compared outcomes of those patients completing and not completing interdisciplinary care.[95] Non-completers of interdisciplinary rehabilitation for chronic pain were found to have poor socioeconomic outcomes one year after discharge from treatment, including poorer work status and greater utilization of healthcare. Patients who did not complete the program were also seven times more likely to undergo post-treatment surgery. Those who completed the program were ten times more likely to return to work and seven times more likely to continue working after 12 months of treatment. Non-completers, as a group, had a greater prevalence of comorbid health problems, greater rates of smoking, ongoing financial disputes related to disability, negative relationships with their employer, and longer pre-treatment length of disability time. Gagnon et al. studied a similar intensity interdisciplinary program and found operant factors contributing to early discharge for injured workers (31%) participating in a functional restoration treatment program and included inconsistencies in performance, noncompliance with self-management techniques, disagreement with goals, and distressful or belligerent behavior.[96]

Interdisciplinary Pain Program Accreditation

International commissions, state workers' compensation bodies and mandated legislative acts, and specific insurance payer groups or plans may certify or accredit interdisciplinary programs or deem specific program centers of excellence, enabling patients to receive treatment as a covered benefit of service. CARF accredits thousands of aging services, behavioral health, opioid treatment programs, and medical rehabilitation programs, including inpatient and outpatient interdisciplinary pain programs across the United States and Canada. CARF describes interdisciplinary pain rehabilitation programs (IPRPs) that provide outcomes focused, coordinated, goal-oriented team services, with strict criteria related to the medical director, behavioral health, and team member training, including specialty certification in pain management and experience in team-based care. CARF IPRPs should focus on the unique needs of persons with persistent pain, including minimizing impairments and secondary complications, reducing activity limitations, maximizing participation and quality of life, and decreasing environmental barriers.[97] CARF standards also include admission and discharge criteria, program components, integration of team conferences, communication with stakeholders involved in an individual's care, as well as community-directed interventions of the interdisciplinary team, including education and training for external stakeholders; and strict ongoing assessments of ongoing

programs, program development, resource utilization management, financial planning, and decision making. After the proliferation of IPRPs in the 1980s, a decline was seen from over 200 accredited CARF programs in the late 1990s to 87 in 2019 and 74 in 2020. Several programs may voluntarily choose not to be accredited for various reasons, including financial or administrative burdens, but CARF accreditation remains a proxy for the relative number of programs available. An increase in CARF accredited programs has been seen in the VA/DoD (currently 20 programs) and now accounts for almost one-fourth of all programs in the United States. This may be related to the 2009 Directive, realizing the value of these programs in a closed system and providing valuable, comprehensive, and patient-centered care for veterans.

The availability of interdisciplinary care may vary depending on the state where care is being provided, including the state and injured workers' benefits system, insurance structure, and fee schedules. The State of Washington Labor and Industries Department, for example, provides and coordinates care for injured workers and describes specific interdisciplinary pain programs for patients covered by the state workers' compensation insurance plan and/or covered under self-insured and managed care plans.[98] The "Structured Intensive Multidisciplinary Programs" or SIMP's are "structured" in that they deliver care through regularly scheduled modules of assessment education and treatment. They are "intensive" and include daily treatment, six to eight hours per day, five days per week, for up to four weeks. They are "multi-disciplinary" or interdisciplinary, including medical management, behavioral health, physical and OT, and vocational services depending on the worker's needs. SIMPs are a "program" in that they provide outcomes focused, coordinated, goal-oriented team treatment. Similar programs and rules are found across the United States in many states, where the treatment of injured workers is legislated, managed, and delivered at the individual state level. Many programs may or may not need to be accredited by CARF or other accrediting bodies. The state of Ohio, for example, requires ongoing re-accreditation by CARF to provide care for injured workers.[99] Providers need to be familiar with their state laws and potential interdisciplinary program availability and resources.

Conclusion

Interdisciplinary care is a true team-based approach based on a patient-centered biopsychosocial model of care. Programs have evolved since the early years of "multi-disciplinary" rehabilitation programs started by John Bonica, Wilbert Fordyce, and others in the 1970s. Functional restoration and structured interdisciplinary treatment evolved and was later championed by Loeser, Mayer, Gatchel, and many others, along with developments in the fields of health psychology and evolution of knowledge around the underlying and complex nature of persistent pain and high-impact chronic pain. Comprehensive pain management relies on an appreciation for complex physiologic changes, including central nervous system sensitization and behavioral and psychosocial factors, necessitating a biopsychosocial approach. This chapter reviewed the SFRP at the Swedish Health System as an example and as a point of reference. The chapter only included an overview of other academic and private interdisciplinary programs from around the United States, demonstrating variability in scope of practice, disciplines used, payer mixes, and novel delivery models.

Interdisciplinary treatment can be described as involving four phases: the comprehensive interdisciplinary assessment, usually provided by a pain medicine specialist, pain psychologist, and vocational counselor; the pre-programing phase, where patient issues are clarified and patients are stabilized for formal self-management training; formal interdisciplinary treatment in a structured program; and finally, the post-program follow up care and maintenance phase.

Pain medicine specialists are commonly the leader or co-leader of the treatment team, helping to coordinate care, setting realistic goals, providing feedback on an individual's progress, and identifying and clarifying pain-related diagnoses. Team disciplines, in general, include physical and OT, behavioral medicine (pain psychology, RT, counseling), nurse education, and vocational services. A key concept of interdisciplinary management is an emphasis on patients learning self-management skills, a greater understanding of persistent pain, the nervous system, sensitization, and how to integrate and apply self-management skills (i.e. exercises and stretching, activity pacing, relaxation, mindfulness, aerobic exercise, and therapeutic movements, such as Tai Chi and yoga) into an individual's daily routine, work, and leisure pursuits. Programs offer a positive treatment milieu to help support patients and guide them to learn new skills to better manage their high-impact chronic pain condition along with traditional multimodal treatments such as medication approaches and interventional procedures, to better and more safely decrease pain and improve function and quality of life. The programs also provide a structure to help clarify issues around opioid use and other controlled substance problems and are an ideal environment to assist patients who need tapering and detoxification as they learn other non-pharmacologic skills to manage their pain and return to higher levels of function.

Efforts to improve patient-centered comprehensive pain care in response to the growing prevalence of high-impact chronic pain, behavioral health disorders, substance, and opioid use disorders, and the drug overdose epidemic should focus on increasing access to interdisciplinary care. In the future, these programs should be a more integral part of typical pain management service lines and pain treatment centers to help patients learn new skills to manage pain better and return to greater levels of function.

IPRPs have been shown to be effective in returning patients to work and have been positioned clinically within the continuum of care for injured workers, including work conditioning and work hardening treatment programs. The reader is referred to other resources more specific to the rehabilitation of injured workers, as this important area was not specifically emphasized in this chapter.[100]

Key Points

- Interdisciplinary pain rehabilitation incorporates a team-based approach, built on a biopsychosocial model of care delivered to patients in structured, primarily outpatient settings that incorporate PT and OT, pain psychology, RT, medical management, and pain education.
- A: multi-disciplinary" team-based approach was developed by John Bonica in the 1960s and advanced in collaboration with Bill Fordyce, incorporating behavioral approaches. Programs were formalized into structured interdisciplinary programs later by John Loeser and many others and expanded to include

functional restoration approaches led by Tom Mayer and Robert Gatchel, all of whom focused on a patient-centered, biopsychosocial approach.

- A growing area of PT directed education within an interdisciplinary pain rehabilitation program includes PNE. PNE deemphasizes pathoanatomic educational content with a focus more on teaching patients about the complex neurologic, psychological, and physical contributors to the development of pain such as pain as an "alarm system" warning of actual or potential tissue damage; pain's influence on thoughts, emotions, actions, and activities; signal transmission, including synapses and neurotransmitters, ability to modify the excitability of peripheral nerves, and the brain's role in the production of pain and the influence of beliefs, emotions, and attention on pain production.
- The four phases of interdisciplinary care include the comprehensive assessment: pre-programming, where necessary workup or stabilization of medical issues or psychiatric function; formal interdisciplinary pain management participation; and post-program or maintenance classes.
- The primary clinical focus of OT within an interdisciplinary program includes ergonomic and posture training, IADLs assessment and training, and learning new skills related to activity pacing. Pacing includes determining the amount of activity that can be done without causing a pain flare up, allowing one to be more productive, conserve energy for goal-oriented activities, and be able to manage their overall pain better.
- Movement therapies may also be included in many interdisciplinary programs and may include a range of Eastern and Western mindful-based practices that help to promote patient-centered proactive participation in one's health and may include the practice of Tai Chi, Qigong, Yoga, Pilates, and the Feldenkrais Method.
- Many chronic pain patients present with varying levels of psychosocial distress, such as depression and anxiety, elevated catastrophic thinking, maladaptive ideas about their pain condition, and previous or active physical or psychological trauma. Pain psychology emphasizes CBT, mindfulness training, acceptance, and commitment therapy provided in individual and group sessions.
- Relaxation therapy uses evidence-based techniques to help patients release or reduce mental, emotional, and physiologic tension. Common relaxation techniques that patients may learn in interdisciplinary treatment include diaphragmatic breathing (DB), progressive muscle relaxation (PMR), grounding exercises, and autogenic training (AT).
- Recent initiatives and legislative acts supporting multi- and interdisciplinary care include the NPS, the CDC Chronic Opioid Management Guideline, the National Academies of Medicine report, the HHS Pain Management Interagency Task Force report, and the National Governor's Association report.
- Several meta-analyses and individual studies have demonstrated the efficacy of IPRPs to decrease pain, improve psychosocial function, and decrease and/or help taper off chronic opioids and return patients to work.

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5

The Healthcare Policy of Pain Management

THOMAS R. VETTER

Rationale for Pain Management Being a Healthcare Policy Priority

Chronic pain is a major cause of suffering, disability, lost productivity, and diminished quality of life across the entire life span and around the world.[1] The global burden of chronic pain is increasing in parallel with the aging worldwide population and the greater prevalence of pain-associated medical conditions like diabetes and obesity.[2]

In its seminal report, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research," the Institute of Medicine (IOM) observed that more Americans suffer from chronic pain than the combined prevalence of heart disease, cancer, and diabetes.[3]

According to the United States Centers for Disease Control and Prevention, based upon 2016 National Health Interview Survey data, an estimated 20.4% (50.0 million) of adults in the United States have chronic pain, and 8.0% (19.6 million) of adults in the United States have high-impact chronic pain.[4] Similarly, 27% of the European adult population are affected annually by a chronic pain condition.[5]

The individual and societal costs of chronic pain are multifaceted and extensive. It is essential that well-informed healthcare providers and health policymakers are fully cognizant of these costs (Table 5.1).[6,7] Notably, chronic pain-related costs borne by individual patients and their families—such as uninsured treatments, informal care, and intangibles related to loss of quality of life—are unquestionably substantial but difficult to measure, and hence often under recognized and underappreciated.[6,7]

The societal impact of nearly 30% of American adults having a chronic pain condition includes associated (1) annual direct medical costs of US$261–$300 billion and (2) lost productivity costs of US$297-$336 billion—totaling upwards of $US635 billion dollars per year.[1,8,9]

The estimated direct and indirect healthcare costs for chronic pain disorders in the European Member States vary between 2% to 3% of gross domestic product across the European Union. For 2016, this estimate would correspond up to 441 billion Euros.[10]

Even in a country like Canada, with its more constrained, government-controlled, universal health insurance, the most recently estimated mean total yearly expenditure of CDN$5177 per adult with chronic pain equates to an estimated total annual economic burden of chronic pain of CDN$7.2 billion for all of Canada.[11]

Based upon a series of focus groups of key stakeholders from across the United States, the Pain Action Initiative: A National Strategy (PAINS) originally identified six major themes regarding chronic pain (Table 5.2)[12]—all of which speak to interconnected ethical, economic, and healthcare policy aspects of chronic pain.

Subsequently, the Pain Management Best Practices Inter-Agency Task Force was convened by the United States Department of Health and Human Services in conjunction with the United States Department of Defense and the United States Department of Veterans Affairs, along with the Office of National Drug Control Policy, to address acute and chronic pain, especially in light of the ongoing opioid crisis. This Task Force was mandated both (a) to identify gaps, inconsistencies, and barriers and (b) to make updated recommendations for current best practices in managing chronic pain (Table 5.3).[13]

A greater prevalence of chronic pain in the United States has been reported among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents.[4] Furthermore, such vulnerable groups of patients—specifically, children, the elderly, the indigent and uninsured, certain racial minorities, and those with major chronic comorbidities (including mental health disorders)—are also at higher risk of inadequate pain management.[12,14]

By many accounts, patients with chronic pain in the United States and around the world continue to face a major burden, and often an attendant health crisis, because of persistent major challenges in obtaining adequate care—resulting in profound physical, emotional, and societal costs.[3,15,16] Pain management thus has a myriad of major healthcare policy factors and implications, some of which will be discussed further in this chapter.

Corporatization of American Pain Medicine: Its Implications for Widening Pain Care Disparities

In his January 1961 farewell address to the country, United States President Dwight D. Eisenhower warned the nation of the widely unrecognized threat to American democracy from the emerging military-industrial complex.[17] In a similar vein, Arnold Relman, the former editor of *The New England Journal of Medicine*,

TABLE 5.1 The Multifaceted and Extensive Individual-Borne and Societal Costs of Chronic Pain[6,7]

Costs of interventions and therapies for treating pain and securing pain relief
Costs incurred for additional primary care and specialty consultations as a result of ineffective interventions being provided
Costs for patients and their families to access conventional or alternative therapies because of a lack of appropriate facilities within their localities
Costs resulting from inappropriate self-medication and treatment by patients
Costs of treating and preventing adverse events that arise as a result of prescribing decisions
Costs of disability claims resulting from an individual's inability to work
Costs to employers and economy of reductions in productivity and absenteeism
Costs of providing social support, home care, and respite care to people suffering with pain
Costs of informal care provided to patients by families, including loss of earnings
Costs of intangibles associated with deterioration in the quality of life of patients and their families

TABLE 5.2 Continued Major Themes in Chronic Pain Management[12]

Reducing disparities in access to pain care among the young, elderly, and lower socioeconomic groups
Defining quality of care in pain management
Need to train qualified providers and training programs in pain medicine
Need for evidence-based public policy regarding opioid use and diversion
Need to raise awareness about chronic pain as a disease to prevent stigmatization and discrimination
Promotion of multimodal therapies for pain care as a way of diverting attention from opioid abuse problem

TABLE 5.3 Dependencies for Achieving Current Best Practices and Excellence in Chronic Pain Care[13]

An emphasis on an individualized, patient-centered approach for diagnosis and treatment of pain is essential to establishing a therapeutic alliance between patient and clinician.
A multidisciplinary approach for chronic pain across various disciplines, using one or more treatment modalities, is encouraged when clinically indicated to improve outcomes.
Effective multidisciplinary management of the potentially complex aspects of chronic pain should be based on a biopsychosocial model of care.
Health systems and clinicians must consider the pain management needs of the special populations that are confronted with unique challenges associated with chronic pain.
Risk assessment is one of the four cross-cutting policy approaches necessary for best practices in providing individualized, patient-centered care.
Stigma often presents a barrier to pain care and is often cited as a challenge for patients, families, caregivers, and providers.
Improving education about pain conditions and their treatment for patients, families, caregivers, clinicians, and policymakers is vital to enhancing pain care.
Addressing barriers to access to care is essential in optimizing pain care, including the workforce gap for all disciplines involved in pain management and improved insurance coverage and payment for different pain management modalities.

opined in 1980, the emergence of what he labeled as the "medical-industrial complex" and presciently observed:

> *This new "medical-industrial complex" may be more efficient than its nonprofit competition, but it creates the problems of overuse and fragmentation of services, overemphasis on technology, and "cream-skimming," and it may also exercise undue influence on national health policy. Closer attention from the public and the profession, and careful study are necessary to ensure that the "medical-industrial complex" puts the interests of the public before those of its stockholders.*

The subsequent inexorable rise of this medical-industrial complex has resulted in an immense for-profit American healthcare industry—ranging from proprietary hospital systems, skilled nursing facilities, and nursing homes to diagnostic services, medical devices, hemodialysis, pharmaceutical industry ("Big Pharma"), the insurance industry, home health care, and many other related brand-named activities.[18–20]

The well-established phenomena of corporatization, consolidation, and commoditization are based on the fundamental business principle of maximizing profitability, primarily through improved economies of scale, greater efficiency, and cost containment. These phenomena can apply to the overall healthcare sector through its individual healthcare companies and medical professional practices (Table 5.4).[21–23]

Over the past 40 to 50 years, there has been a widespread corporate transformation in American healthcare.[18,22,24] The original motivating ideology for the corporatization and proprietization of healthcare was a commitment to excellence of care. However, this impetus has been replaced by cost containment and profitability.[21,25] With the concomitant concentration and centralization of healthcare delivery in the United States, the pursuit of profit has become central.[21]

The primary goal of health corporations has become to earn profits, with their justifying mantras of "no margin—no mission" or "no income—no outcome." However, ironically, their corporate product is health care, for which the poor and vulnerable populations have an equal or greater need but often limited or no access. Thus the corporatization of medicine presents a complex moral dynamic across the variables of access, cost, efficiency, and quality of care.[26]

As the corporatization of health care has become more pronounced in the US, it has paradoxically been in part responsible for not only the high cost but also the inconsistency and fragmentation of the medical care and services that Americans receive.[27] Health care in the United States has thus become dominated by a business philosophy whose primary concern is increasing share-

TABLE 5.4 Basic Definitions Used in Corporate Transformation Among Its Financial Stakeholders[22,23]

Corporatization: The acquisition of part or all of the assets of a healthcare company or medical professional practice by private equity firms, venture capital firms, or publicly traded companies
Consolidation: Merger and acquisitions of many smaller healthcare companies into fewer larger ones
Commoditization: Widespread availability of a healthcare related good or service that has reduced the basis for patient-consumer decision making to simply price

holder value rather than providing optimal care and experience for patients.[28] Furthermore, vulnerable groups become more vulnerable when profit becomes the driving force in conceptualizing, organizing, and delivering health care.[26]

The writ large corporate systematization and commodification of medicine has had a knock-on effect on pain medicine.[25,29] Scientific progress continues to increase the understanding of pain mechanisms and availability of effective pain therapeutics. However, the administrative and economic infrastructure that supports—or just as often denies—providing indicated medical services leaves clinicians ever more disempowered to use this knowledge to effectively care for all individuals who are experiencing chronic pain—thus threatening the moral obligation to treat all pain patients safely, effectively, and equally.[29]

There has been an accompanying transformation (devolution) of the "profession" of pain medicine into the "business" of pain medicine,[30] which has been marked by:

- physician complicity in the transformation of pain medicine from a profession to a business;[31]
- the refusal by the health insurance industry to cover multidisciplinary/interdisciplinary pain management programs;[32]
- the increase in pain management spending without any evidence of improved patient outcomes;[33]
- the overutilization of interventional procedures and spine surgery by physicians who have questionable relationships with industry;[34]
- the innate, continued conflict of interest relating to industry and its impact on pain education;[35] and
- the corporatization of American pain management and the resulting benefits to certain special interests and concomitant increases in disparities in pain care.[26]

Ideally, pain medicine depends upon patients having ready access to freestanding or hospital-based clinics, interdisciplinary care teams with diverse providers and specialty services, diagnostics, interventions, medical products and devices, as well as pharmaceuticals—but each vital component poses layers of bureaucratic, financial, and non-access related barriers.[26]

The biopsychosocial model of pain has been well-recognized as an optimal approach to the assessment, treatment, and prevention of pain.[36–39] This comprehensive, multidimensional approach to chronic pain equally considers the multiple biologic, psychological, and social factors frequently associated with chronic pain (Table 5.5).[40]

However, a narrow-minded vision of pain treatment in the United States—once again, more driven mainly by market forces than evidence—has resulted in a decreasing number of multidisciplinary pain management programs. The practice of pain care that focuses predominantly on pharmaceutical agents and biomedical interventions is inaccurately redefining pain as a nociceptive phenomenon—thus undermining the perceived importance

TABLE 5.5 Factors Associated With The Development of Chronic Pain[40]

Factor	Elements
Demographic	Age Gender Ethnicity and cultural background Socioeconomic background Employment status and occupational factors
Lifestyle and behavior	Smoking Alcohol Physical activity Nutrition Sunshine and vitamin D
Clinical	Pain Multi-morbidity and mortality risk Mental health Surgical and medical interventions Weight Sleep disorders Genetics
Other	Attitudes and beliefs about pain History of violent injury, abuse, or interpersonal violence

of its psychosocial dimensions, which are direct determinants of the tremendous direct and indirect costs of pain to the individual and society.[26] Therefore many pain medicine practices in the United States have become nothing more than profit-driven, "block shops" and "pill-mills" that are staffed and owned by entrepreneurial "needle jockeys" and "pill-pushers" who enjoy very large profit margins and high professional incomes.[41]

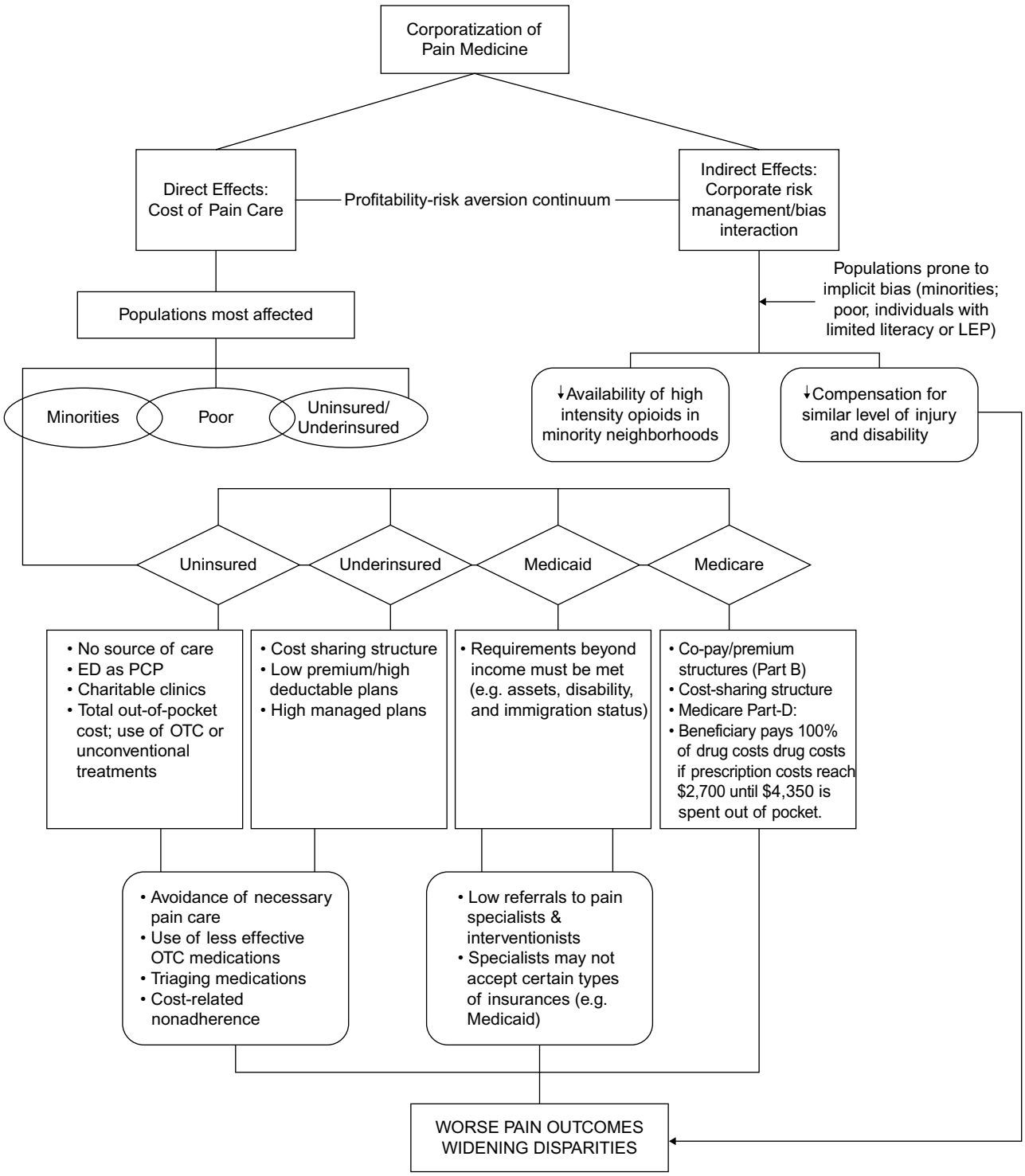
While the corporatization, consolidation, and commoditization of pain medicine have implications for many populations, three groups are the most vulnerable to its effects: the poor, minorities, uninsured, and underinsured. The corporatization of pain medicine in the United States has had major implications, especially in widening the disparities in pain care (Fig. 5.1).[26] Specifically, the highly profit-oriented mindset and culture within the current practice of pain medicine has resulted in the amplification of the already-existing disparities in care by driving up its costs and limiting options, thereby making comprehensive pain treatment inaccessible to more Americans.[25]

Although the corporatization of American medicine may originally have been well-intended—ostensibly, to promote competition, and thereby to drive down healthcare costs—the actual consequence of this widespread phenomenon has been an increase in human pain and attendant suffering.[25]

Pain Management as a Global Public Health Priority and a Human Right

The initial 2013 Global Burden of Disease Study,[42] and its subsequent updates undertaken in 2015, 2016, and 2017,[43–45] have provided valid, consistent, and striking evidence of the substantial, global morbidity and disability burden of pain, and diseases associated with pain, in both the developed and developing countries.[46]

Quite importantly, although some infectious diseases have decreased in prevalence since 1990, the burdens associated with chronic pain are overall increasing. This is partly because of dominant



• **Figure 5.1** How poverty, minority status, and un/underinsurance widen pain treatment disparities in the United States (Reprinted with permission:[16] *ED*, Emergency department;*LEP*, limited English proficiency; *OTC*, over-the-counter; *PCP,* primary care provider.

demographic forces like the aging of populations across the developed countries and similarly increased survival into middle and old age in the developing countries—resulting in not only a growing population size but also a mounting prevalence of chronic diseases.[46]

Humans are thus living longer, but with more chronic disease and disability. An unprecedented transition is occurring from a world with predominantly communicable diseases to one with chronic disease and disability, with implications for the welfare of people worldwide. However, health systems and economies are not prepared for this transition. Instead, the discordance between health system responses and the changing population needs is worsening, as are health inequalities.[47]

Not surprisingly, the World Health Organization (WHO) and the United Nations (UN) have estimated (1) that over 75% to

80% of the world's population receives inadequate treatment for moderate to severe pain and (2) that at least 5 billion people live in countries with minimal to no appropriate access to governmental controlled analgesics like opioids and psychotropics.[48–50]

Given this enormous worldwide burden, pain should presumably represent a continued major global public health concern.[51,52] Yet until only recently, pain management has been relatively neglected by national governmental agencies and international non-governmental organizations (NGOs).[53–59]

Acute, chronic, and cancer pain collectively represent the often unreported and hence silent dimension of many of the worldwide causes of adult and pediatric morbidity and mortality.[46,55] Although acute pain may reasonably be considered a symptom of disease, illness, or injury, chronic and recurrent pain is a specific healthcare problem—a disease in its own right.[52,60] It has been persuasively posited that this pervasive view of chronic pain as a symptom of disease, rather than a disease state in itself, has contributed to the paucity of public health and health policy attention and funding that chronic pain has historically received.[12,51]

Consequently, the WHO, the International Association for the Study of Pain (IASP), and the European Federation of the IASP Chapters jointly declared in 2004 that such widespread, inadequately treated chronic pain must not be tolerated and that the relief of pain should be a universal human right.[53–55,61] In 2010, the IASP issued its "Declaration that Access to Pain Management is a Fundamental Human Right" ("Declaration of Montreal") (Table 5.6), which in addition to emphasizing that chronic pain is a disease entity, reaffirmed the basic human right to access effective pain management and the obligation of governments and healthcare institutions to establish laws, policies, and processes that help promote—not inhibit—access to pain management.[60,62]

Fortunately, the concept of access to pain management as a human right has recently gained increasing currency.[63] Beginning as individual-level advocacy ("cries in the dark"), this concept was embraced by the disciplines of pain medicine and palliative care and by mainstream human rights organizations (e.g., Human Rights Watch). By 2019, the UN and regional human rights bodies had accepted the concept and incorporated it into their key human rights reports, reviews, and standards.[63]

The two ultimate aims of this sustained global pain initiative have been (1) to inform international, regional, and national health policymakers about the personal burden and the economic costs of chronic pain and (2) to educate physicians and allied healthcare professionals about pain assessment and treatment to promote higher standards of care worldwide.[54,60] Similar attention has been focused on receiving effective palliative care being a universal, international human right.[58,64–66] Lastly, the denial of adequate pain treatment, when used as a form of punishment or torture, is a grossly egregious human rights violation.[67]

The Continued Need to Achieve a More Equitable and Balanced, Worldwide Access to Analgesics and Effective Analgesia

Pain is a universal, multicultural experience that affects all people, regardless of demographics or geography. However, its inadequate treatment and adverse effects are not equally distributed worldwide.[51,63]

Despite international human rights laws, calls for the reform of laws and policies inhibiting local, regional, and national access to pain treatment—as well as the attendant obligation of sovereign states to provide their citizens access to pain relief medicine—barriers still commonly exist to patients' accessing effective pain treatment and palliative care globally (Table 5.7).[68,69]

TABLE 5.6 International Association for the Study of Pain "Declaration that Access to Pain Management is a Fundamental Human Right" ("Declaration of Montreal")[60]

Article 1. The right of all people to have access to pain management without discrimination.

Article 2. The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed.

Article 3. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals.

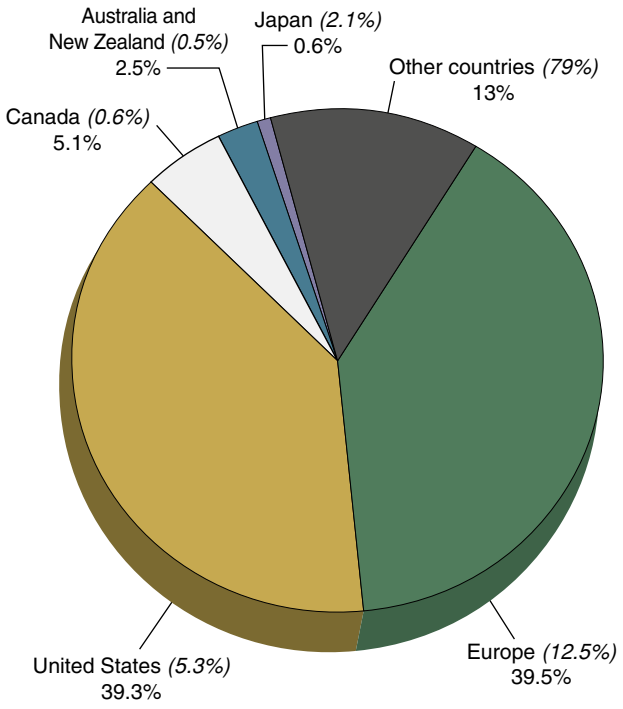
As a result of these barriers, receiving even basic treatments, like oral analgesics, including opioids (e.g. morphine) for cancer pain, and anti-epileptic and anti-depressant drugs for neuropathic pain, remain widely disparate and commonly deficient worldwide.[16,70]

Even though such simple, cost-effective treatments exist, a major gap still continues between the increasingly sophisticated understanding of the mechanisms and pathophysiology of pain and its continued widespread inadequate management.[16,70] As poignantly observed by the authors of the 2018 Lancet Commission on Global Access to Palliative Care and Pain Relief report:[70]

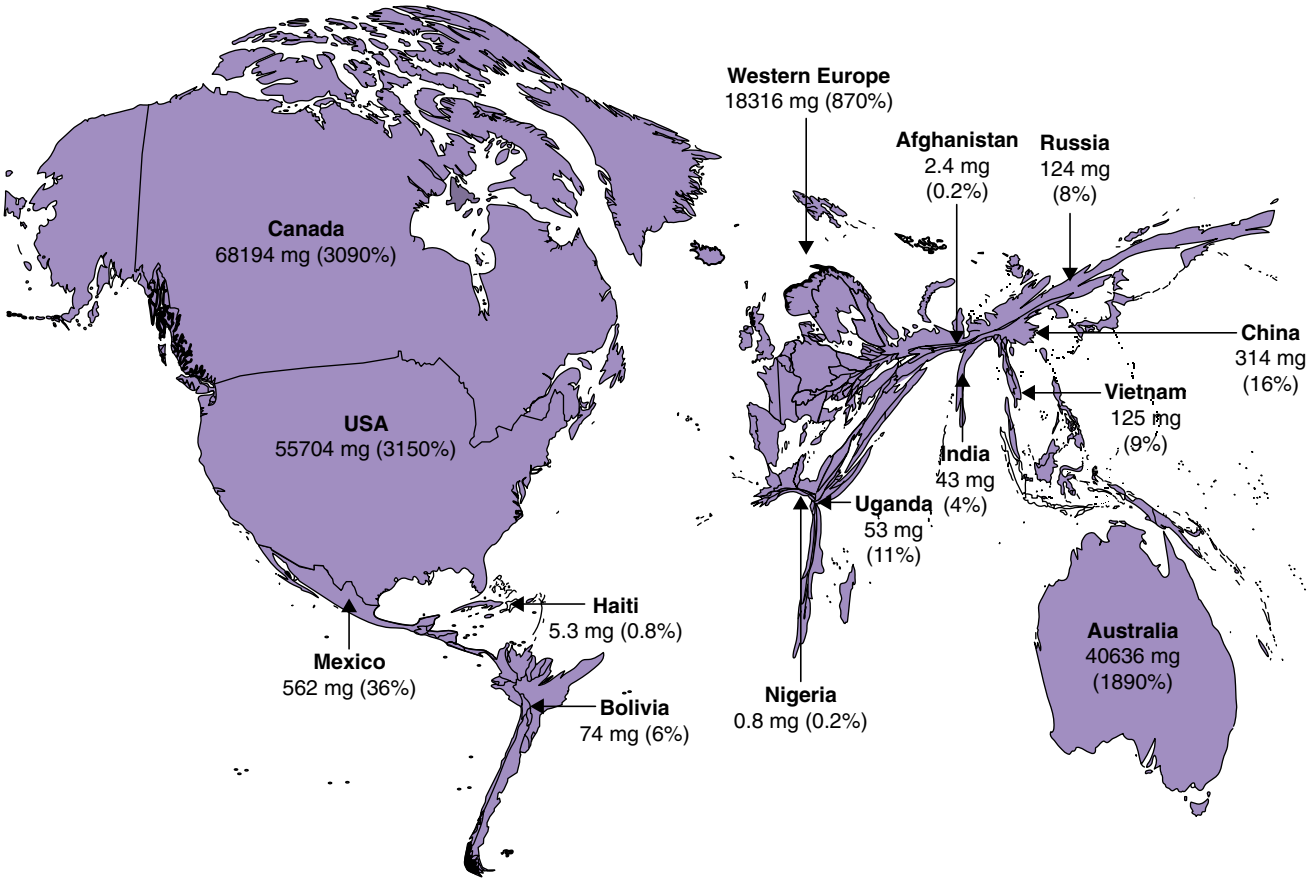
> *"Poor people in all parts of the world live and die with little or no palliative care or pain relief. Staring into this access abyss, one sees the depth of extreme suffering in the cruel face of poverty and inequity. The abyss is broad and deep, mirroring relative and absolute health and social deprivation… The fact that access to…inexpensive, essential, and effective intervention is denied to most patients in low-income and middle-income countries (LMICs) and in particular to poor people—including many poor or otherwise vulnerable people in high-income countries—is a medical, public health, and moral failing and a travesty of justice."*

Greater than 61 million people worldwide experience about 6 billion days of serious health-related suffering annually, which could be alleviated with proper and adequate access to analgesics, palliative care, and pain relief. However, palliative care, in particular, is limited or nonexistent in most parts of the world.[71] The "access abyss" called out by the 2018 Lancet Commission is so stark that 50% of the poorest populations in the world live in countries that receive only 1% of the opioid analgesics distributed globally. By contrast, 10% of the richest populations in the world live in countries that receive nearly 90% of the opioid analgesics distributed globally.[71]

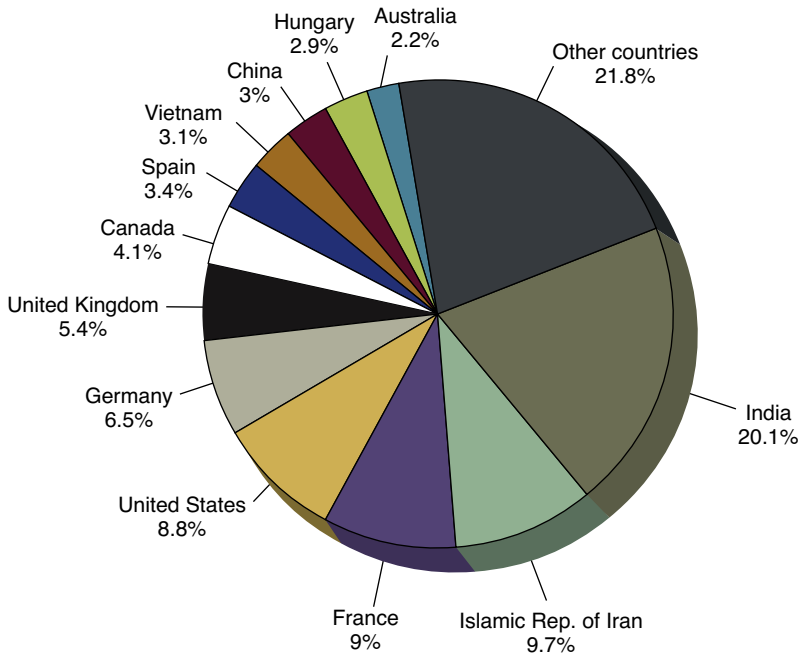
According to the International Narcotics Control Board (ICNB), the country-level differences and maldistribution in the consumption levels of opioids continue to be very significant. In 2018, the greatest share of morphine consumed legally worldwide occurred in the European countries as a whole (39.5%) and the United States (39.3%), followed by Canada (5.1%), Australia and New Zealand (2.5%), and Japan (0.6%) (Fig. 5.2).[72] In stark contrast, 79% of the world's population—mainly people living in low-income and middle-income countries—consumed only 13% of the total amount of morphine used for the management of pain and suffering in 2018, or 1% of the 388 tons of morphine manufactured worldwide (Fig. 5.3).[72]



• **Figure 5.2** Distribution of nation-level, legal morphine consumption in 2018 according to the International Narcotics Control Board (INCB) <http://www.incb.org/>. Note: The percentage in parentheses refers to the share of the total population of all the countries that submitted data on morphine consumption. (Reprinted with permission: **Will need to obtain permission to reprint**).[72]



• **Figure 5.3** Distributed opioid morphine-equivalent (morphine in mg/patient in need of palliative care, average 2010-13), and estimated percentage of need that is met for the health conditions most associated with serious health-related suffering, based upon data from International Narcotics Control Board (INCB) <http://www.incb.org/>. (Reprinted with permission: **Will need to obtain permission to reprint**).[70]



• **Figure 5.4** Distribution of nation-level, legal codeine consumption in 2018 according to the International Narcotics Control Board (INCB) <http://www.incb.org/>. (Reprinted with permission: **Will need to obtain permission to reprint**).[72]

In 2018, the country with the highest percentage of the global consumption of hydrocodone (99.1%), oxycodone (63.4%), and hydromorphone (44.9%) continued to be the United States.[72] In 2018, only codeine consumption was more evenly distributed worldwide (Fig. 5.4).[72] This is ironic given that codeine is a prodrug, which lacks intrinsic analgesic properties without its variable hepatic conversion, because of genetic polymorphism, into morphine.[73]

While opioids remain the mainstay for the treatment of moderate and severe pain, in many countries, the legal availability and legitimate consumption of these analgesics appear grossly insufficient. Historically, various NGOs, including experts from the WHO and ICNB, have published opioid analgesic metrics. These organizations have advocated for legal, legitimate opioid consumption at a level considered adequate, as based on the actual consumption in the most developed countries.[74]

A recent study examined the current adequacy of clinical opioid consumption.[74] The authors analyzed data for 18 controlled opioid medications, primarily used as analgesics, and developed an Adequacy of Opioid Consumption (AOC) Index. The average consumption of the 20 most developed (highest income) countries for 2015 was equated to an AOC Index of 100. An AOC Index of 100 or higher was considered indicative of adequate consumption.[74] The average opioid analgesic consumption of the 20 countries with the highest Human Development Index increased from 84 morphine milligram equivalents per capita in 2000 to 256 morphine milligram equivalents per capita in 2015. The extremes in 2015 were Germany (AOC Index of 304) and Nigeria (AOC Index of 0.0069), with a 44,000-fold difference, further evidence of the continued very problematic disparity in worldwide opioid analgesic consumption.[74]

Nevertheless, as promulgated now for over two decades by the Pain & Policy Studies Group at the University of Wisconsin Carbone Cancer Center, School of Medicine and Public Health, improving global pain relief requires achieving a more pragmatic yet balanced access to opioids worldwide. "Balance in the [health] policy context refers to international, national, and state policies that strive to ensure both the adequate availability of pain medication for patient care and the avoidance of their diversion and abuse."[69]

The Need for a More Rational Strategy and Equitable Approach to Prescribing Chronic Opioids in the United States

While many worldwide needlessly suffer, prescribing opioids for chronic non-cancer pain has tremendously but irrationally escalated in the United States.[49,50,72] Furthermore, this exponential use of opioids for chronic non-cancer pain in the United States has outpaced the availability of rigorous scientific and epidemiologic evidence of the benefits versus harms of these medications.[75–78]

There has certainly been an abundance of attention focused on the ensuing "opioid epidemic" ("opioid crisis") in the United States.[79–84] The still expanding opioid epidemic in the United States lies at the intersection of two major public health challenges: (1) reducing the continued and unnecessary suffering and burden from pain and (2) containing the rising toll of harms associated with the aberrant use of opioid medications.[85] Successfully addressing both these pressing challenges requires a substantial investment in surveillance and research on several fronts—in addition to a well-coordinated healthcare policy response by federal, state, and local agencies along with other stakeholder organizations.[85]

Initially fueled by greater availability and consumption of prescription pharmaceutical opioids, an increasing number of opioid overdoses in the United States are now resulting from less expensive heroin and illicitly manufactured fentanyl and fentanyl analogs.[82] Effectively addressing this current second wave of the opioid epidemic in the United States requires (1) mitigating the

stigma associated with an opioid use disorder and its treatment, (2) increasing access to efficacious treatment options—specifically, methadone and buprenorphine, and (3) reducing opioid overdose fatalities via the wide distribution of the opioid antagonist and overdose reversal agent naloxone.[82]

The escalating overdose deaths and attendant declines in life expectancy in the United States mandates the adoption of a comprehensive public health approach to the opioid epidemic.[86] Successfully addressing the challenges posed by the opioid epidemic requires an integrated, translational approach that combines the contributions of neuroscience, pharmacology, epidemiology, treatment services, and prevention strategies. It also is crucial to integrate interventions across settings—including health care, justice, education, and social service systems.[86] This innovative approach[86] has four interconnected goals:

- recognizing and addressing the social determinants of health and disease;
- applying person-centered approaches for prevention and treatment;
- bridging the gap between implementation science and practice; and
- using data to build learning systems of care relevant to public health approaches to address the opioid crisis.

A sustained and coordinated effort is thus warranted, which is (1) comprised of multipronged, aligned federal and state policies and initiatives and (2) manifested via regulations, laws, funding, and guidelines.[87] Furthermore, population health research is needed to evaluate the impact and potential unintended consequences of any increased legislation and regulation.[87,88] Ultimately, new pain management-related policy and funding can provide the path to new treatments and models of care that can reduce the impact of pain and opioid proliferation as a dual, interdependent public health crisis in this country.[87]

As it evolved from the Pain Action Initiative: A National Strategy (PAINS),[12] the National Pain Strategy (NPS)[89] aimed to serve as the first comprehensive approach to address pain and provided a roadmap with broad and specific broad policy implications.[87] Released in 2016, the NPS[89] focused on six primary areas for improvement:

- population research
- prevention and care
- disparities
- service delivery and payment
- professional education and training
- public education and communication

Although much has been accomplished to date across all six of these NPS domains, the intercurrent transitions in federal and state political power and priorities, available data and funding, and opioid epidemic continue to hamper implementation of the NPS. To their credit, the NPS collaborators have undertaken a thoughtful, interim, comprehensive strengths-weaknesses-opportunities-threats self-analysis, which provides a transparent progress report and valuable experiential, programmatic insights.[87,90]

Even in countries like the United States with its at least ample, if not overabundant, supply of opioids, there are inconsistent prescribing patterns and thus frequently disparate and inadequate access to opioids. As with many other elements of the United States healthcare system, there are racial, socioeconomic, and age disparities in pain assessment and opioid prescribing patterns, with minorities, the poor, and the elderly less likely to access needed controlled substances.[91–95] In many large United States medical centers, such marginalized patients with a legitimate need for opioids are customarily passed around from clinic to clinic. Thus, out of necessity, such patients frequently visit emergency departments, where pain assessment and treatment are widely variable and inadequate, and where racial disparities in opioid prescribing also exist.[96–100]

An innovative, pharmacy-primary care–based chronic opioid management program (an "Opioid Renewal Clinic") for such high-risk patients was successfully implemented at Philadelphia Veterans Affairs Medical Center.[101–103] To be more widely applied, this comprehensive practice model requires close collaboration between primary care physicians and pain medicine specialists.[104] However, there is little apparent support for such a labor-intensive, comparatively low margin program among non-governmental healthcare administrators, interventional pain practitioners, and for-profit health corporations.

This notwithstanding, in a 2017 themed issue of *Anesthesia & Analgesia* focused on the opioid epidemic (crisis),[84] Brown and Sloan[105] very insightfully observed in their editorial:

> *In light of this public health problem, chronic pain physicians have often been maligned as the root cause of addiction and death because of good faith efforts to treat selected patients suffering long-standing pain with opioids. But, anesthesiologists practicing chronic pain medicine do not prescribe the most opioids, and the multidimensional management most often practiced by these clinicians appears to be a paradigm for responsible opioid treatment of patients with all types of pain. Chronic pain physicians must take the lead as educators of the entire field of medicine on the appropriate and comprehensive management of acute and chronic pain.*

Pain is fundamentally a significant personal and public health problem, which calls for policy, regulatory, statutory, and funding changes at the national, state, and local levels to reduce the prevalence of insufficient, ineffective, and disparate pain treatment while concomitantly mitigating the risk of inadvertently increasing the use of treatment like opioids that can result in personal and public harm.[87]

The Need for a More Comprehensive Approach to Chronic Pain-Related Mental Health in the United States

As noted earlier, the biopsychosocial model of pain has been well recognized as an optimal approach to pain management.[36–39] Such a comprehensive, multidimensional approach to chronic pain equally considers the multiple biologic, psychological, and social factors that are frequently associated with chronic pain (Table 5.5).[40]

Moreover, mental illness, despair borne of economic hardship and uncertainty, and societal pressure, especially among adolescents and young adults, also contribute to the misuse and abuse of opioids.[105] Specific risk factors for opioid misuse or addiction include past or current substance abuse, untreated psychiatric disorders, younger age, and social or family environments that encourage misuse.[106] These factors further complicate the rather dismal current picture of the national opioid epidemic as a personal and public health quagmire.

Chronic pain patients often have a psychiatric disorder that negatively influences their response to treatment. Even if they do not meet the formal diagnostic criteria for a psychiatric disorder, many chronic pain patients also have dysfunctional pain-related beliefs and pain coping strategies.[107]

TABLE 5.7 Barriers to Patients' Accessing Effective Pain Treatment and Palliative Care Globally[68]

The failure of governments to put in place functioning drug supply systems
The failure to enact policies on pain treatment and palliative care
Poor training of healthcare workers
The existence of unnecessarily restrictive drug control regulations and practices
Fear among healthcare workers of legal sanctions for legitimate medical practice
The unnecessarily high cost of pain treatment

Studies analyzing data from pain clinics, general population surveys, and health insurance administrative databases have reported that not only traditional adult but also adolescent and younger adult patients with a common psychiatric problem like depression, anxiety, and substance use disorder, are more likely to be prescribed opioids for chronic non-cancer pain than patients without a mental disorder.[108–110]

The current opioid epidemic in the United States has highlighted the substantial yet largely unfunded and unmet need for more consistent and effective psychiatric and psychosocial services—the so-called presently "missing p"—in chronic pain care.[108]

Valid psychosocial screening for depression, anxiety disorder, and substance use disorder should be routine components of the initial assessment for all patients who present for chronic pain management. The initial clinical evaluation should also include an assessment of the patient's functional status, specifically, daily physical activities, personal environmental and social wellbeing, and occupational status.[108] When implemented in conjunction with physical rehabilitation modalities, the timely treatment of any identified psychiatric comorbidities with appropriate pharmacotherapy, cognitive behavioral, and supportive therapy can often lead to improvements in a patient's physical and psychosocial functioning—thereby avoiding the problems associated with long-term opioid use.[108]

Conclusions

Given the widespread and substantial human and financial impact and burden of pain, pain management economics and health policy are inextricably linked. As noted earlier, all healthcare systems—across the entire socioeconomic spectrum and around the world—are confronting the same fundamental health economic and health policy dilemma: How best to allocate finite resources to satisfy seemingly infinite healthcare demands.[111] Ultimately, as observed by a leading healthcare economist, "In a world of budget constraints there are no easy solutions."[112] Nevertheless, clear guidance and recommendations are needed to prioritize and to address these ever-expanding healthcare needs.

Cited at the outset of this discussion, it is fitting to conclude by revisiting the still quite relevant 2011 IOM report, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." It offers a set of underlying principles (Table 5.8), a series of 16 salient recommendations, provides a timeline for implementing them and designates the groups responsible for doing so.[3,113] While focused on the healthcare system in the United States, these IOM findings and recommendations are universally applicable and represent an urgent call for continued action.

TABLE 5.8 Underlying Principles Institute of Medicine (IOM) "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research"[3]

A moral imperative: Effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions.
Chronic pain can be a disease in itself: Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious, separate disease entity.
Value of comprehensive treatment: Pain results from a combination of biological, psychological, and social factors and often requires comprehensive approaches to prevention and management.
Need for interdisciplinary approaches: Given chronic pain's diverse effects, interdisciplinary assessment and treatment may produce the best results for people with the most severe and persistent pain problems.
Importance of prevention: Chronic pain has such severe impacts on all aspects of the lives of its sufferers that every effort should be made to achieve both primary prevention (e.g., in surgery for broken hip) and secondary prevention of the transition from the acute to the chronic state through early intervention.
Wider use of existing knowledge: While there is much more to be learned about pain and its treatment, even existing knowledge is not always used effectively, and thus substantial numbers of people suffer unnecessarily.
The conundrum of opioids: The committee recognizes the serious problem of diversion and abuse of opioid drugs and questions about their usefulness long term but believes that when opioids are used as prescribed and appropriately monitored, they can be safe and effective, especially for acute, postoperative, and procedural pain, and for patients near the end of life who desire more pain relief.
Roles for patients and clinicians: The effectiveness of pain treatments depends greatly on the strength of the clinician-patient relationship. Pain treatment is never about the clinician's intervention alone, but about the clinician and patient and family working together.
Value of a public health and community-based approach: Many features of the problem of pain lend themselves to public health approaches—a concern about the large number of people affected, disparities in occurrence and treatment, and the goal of prevention cited above. Public health education can help counter the myths, misunderstandings, stereotypes, and stigma that hinder better care.

Key Points

- Chronic pain is a major cause of suffering, disability, lost productivity, and diminished quality of life across the entire life span and around the world.
- The individual and societal costs of chronic pain are multifaceted and extensive.
- It is essential that well-informed healthcare providers and health policymakers are fully cognizant of these costs.
- Patients with chronic pain in the United States and around the world face a major burden because of persistent major challenges in obtaining adequate care, resulting in profound physical, emotional, and societal costs.
- The corporatization of American pain medicine has major implications for widening pain care disparities.
- Pain management is a global public health priority and a human right.
- It is vital to achieve a more equitable and balanced, worldwide access to analgesics and effective analgesia.
- There is a mandate for a more rational strategy and equitable approach to prescribing chronic opioids in the United States.
- There is a substantial need for a more comprehensive approach to chronic pain-related mental health in the United States.

Suggested Readings

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6

Quality Assessment, Improvement, and Patient Safety in Pain Management

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This chapter covers challenges in defining, measuring, and improving quality in pain management as well as patient safety issues. These are in some cases distinct and in others inextricably interrelated. They are each debated on national and international levels, and both are fundamental elements of the daily practice of pain management. The first section considers quality assessment and improvement programs and practical steps to measure quality and create a quality improvement (QI) program in pain practice. The second section discusses the patient safety movement, both on a national scale and in terms of how each pain practitioner can expect to be involved.

SECTION I QUALITY ASSESSMENT AND IMPROVEMENT IN PAIN MANAGEMENT

Quality is a nebulous concept, especially in the realm of healthcare. Within the field of pain medicine, healthcare quality becomes even more challenging to define because pain itself is a highly individualized, subjective biopsychosocial experience that does not easily lend itself to standardized measurement or treatment. Further, pain medicine itself is practiced in many different ways (e.g. pharmacologic, interventional, rehabilitative, interdisciplinary) and many different settings. Whether one examines healthcare at the micro-level (e.g. encounters between patients and providers) or the macro-system (e.g. processes across large academic healthcare organizations), quality is a property of the system. The healthcare system is laden with quality problems related to underuse, overuse, and misuse of services that impact patient safety.[1] In the ensuing two sections, we discuss the topics of quality and patient safety separately. These sections review the practical efforts each pain care provider can make to address those issues at the level he or she can influence.

What Is "Quality" in Healthcare?

Healthcare quality is generally defined in terms of the attributes and outcomes of care provided by practitioners and received by patients.[2] A more specific definition emphasizes the technical aspects and characteristics of interactions between provider and patient.[3] Important attributes of the provider-patient interaction include communication, trust, empathy, sensitivity, and honesty. Technical quality consists of "doing the right thing right."[1] In other words, performing the right tests or providing the right services at the right time in the right way to accomplish the desired outcomes. Outcomes refer to the patient's health status (e.g. changes in pain, physical function, affect, social roles) after treatment concludes.[4] Avedis Donabedian, a physician and founder of the study of quality in healthcare, stated,[5] "quality cannot be judged by technical terms, by healthcare practitioners alone; that the preferences of individual patients and society at large have to be taken into account as well." Donabedian added, "As such, the definition of quality may be almost anything anyone wishes it to be, although it is, ordinarily, a reflection of values and goals current in the medical care system and in the larger society of which it is a part."

Donabedian is also known for developing a practical "structure-process-outcome" framework for conceptualizing quality.[6] Structure is defined as the physical and organizational properties of the setting in which care is provided; the process is what is done for patients, and the outcome is what is accomplished for patients. This three-prong model provides a more comprehensive definition of healthcare quality if we add that which is suggested by Bowers and Kiefe:[7] "quality being the extent to which structure and process maximize the likelihood of good outcomes." Note, the emphasis is on the "likelihood" of good outcomes because high quality care and good outcomes are not necessarily directly linked. As Chassin has described, the vagaries of the human condition mean that good quality medical care can be followed by poor outcomes, and excellent outcomes can occur despite poor care.[8]

In 1990, Donabedian enumerated seven attributes, or "pillars," of healthcare quality:[9]

1. Efficacy-the ability of care to actually improve health.
2. Effectiveness-how well care achieves improvement in health in the circumstances of "everyday practice."
3. Efficiency-the cost of any given improvement in health.
4. Optimality-the point at which incremental increases in care begin to diminish in their return on investment, such that health may be improved, but in a less efficient manner.
5. Acceptability of care to patients-accessibility, the practitioner-patient relationship, amenities of care, patient valuations of care outcomes, patient estimation of care's economic worth.
6. Legitimacy-considerations of the value of care by others than the patient receiving that care, the aspect of societal valuation as mentioned above.
7. Equity-the balance between what individuals and what society considers the appropriate distribution of care and resources.

The degree of attention given to any attribute will vary depending on the aspect of quality being assessed. In any given instance of healthcare delivery, the patient, the provider, and the payer may have very different opinions as to what healthcare quality constitutes. This last lesson should be kept in mind in choosing any single definition of "quality" as most appropriate.

Lohr crafted a definition that the Institute of Medicine (IOM), now termed the National Academies of Medicine, included in its discussion of quality:[10] "quality is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." The IOM National Roundtable on Healthcare Quality revisited this statement in 1998, redefining the phrase "desired health outcomes" to specifically include the health outcomes that patients desire,[11] ushering in the consideration of patient and family satisfaction as a factor in evaluating the quality of healthcare services. However, in the context of pain management, interpreting patient satisfaction is complex. High satisfaction scores are not consistently correlated with traditional outcome and safety indicators and may be associated with increased costs of care.[12,13] Concern over the potential receipt of low patient satisfaction scores impacting pay for performance formulas may have contributed to the overprescribing of opioids[14] in the United States even though opioid prescribing has not been correlated with consumer satisfaction.[15] Patient satisfaction surveys are almost always skewed toward the positive and may be more representative of the quality of the interpersonal relationship between patient and caregiver than the quality of the actual services or their outcomes. Interviews of primary care patients with chronic pain revealed that high patient satisfaction was driven by concrete behaviors including listening, maintaining communication with patients, acting as an access point to comprehensive pain care, providing an honest assessment of the possibilities of pain care, and taking time during consultations with patients.[16]

Drivers of Attention to Quality in Healthcare

Several noteworthy historical influences have led to sustained attention on quality assessment and management in healthcare.

Development of Standards of Care and Accreditation Programs

The debate about the quality of care began more than 100 years ago when a surgeon named Ernest Codman (1869-1940) first proposed standardized outcomes data collection to determine whether care was effective.[17] Codman's ideas swayed the American College of Surgeons to establish a Committee on the Standardization of Hospital Care, ultimately leading to the formation of The Joint Commission (TJC).[18] Interest in care standards grew among public and private insurers as the basis for better and presumably more cost effective coverage policies and quality measurement. Care standards began to be used to shape policy, assess utilization of services, and define and identify inappropriate medical care. In the 1960s, Medicare and Medicaid were established to broaden the population that received healthcare coverage, improve access to care, expand the array of healthcare providers, and decrease cost while improving the quality of care.[19] To help ensure delivery of healthcare in a manner consistent with available standards, accreditation programs such as TJC and the Commission on Accreditation of Rehabilitation Facilities (CARF) became prerequisites for participation in the Medicare program.

Growth of Epidemiology, Information Technology, and Outcomes Research

Growth in clinical epidemiology, information technology, and outcomes research has strongly accelerated the progress of healthcare quality.[20] Use of information and communications garnered from these technological advances helped identify wide variation in the practice and outcomes of care among patients treated for the same healthcare problems in different places and healthcare settings.[2] The awareness of practice variations led to the need to better understand their effect on outcomes. Geographic variations have been uncovered in cost and care, often without linkage between more care and better quality.[21,22] This information fueled interest in outcomes research resulted in new measures of quality, especially in the treatment of chronic illness such as pain, where patient reported outcomes that impact physical, emotional, and social function are important.[23]

The Triple Aim Campaign and Related Concerns over the Cost of Healthcare

In 2007, the Institute for Healthcare Improvement (IHI) created a framework for optimizing health system performance termed the "triple aim" focused on the health of a population, experience of care for individuals within that population, and per capita cost of providing that care.[24] The IHI triple aim entails improvement at all levels of the system and includes identification of target populations, the definition of system aims, and rapid scale testing of models of care and scale up adapted to local needs and conditions. The Patient Protection and Affordable Care Act, passed in March 2010, was designed to address triple pain concerns through a myriad of reforms in healthcare insurance markets.[25] Though the legislation remains controversial, one important objective is to better orient the nation's healthcare system toward health promotion and disease prevention.

The triple aim supports efforts to focus on value for money invested rather than solely on reducing growth or cost reduction. The healthcare spending in the United States grew 4.6 percent in 2018 and accounts for 17.7 percent of the nation's gross domestic product.[26] Ninety percent of the national $3.5 trillion in annual healthcare expenditures are for people with chronic and mental health conditions, many of which include a significant component of pain. It is the perception of many in business, government, and among the public that there is much waste of money in these figures.[27] One example of increased expenditures being disabling low back pain that is partly iatrogenic because of harmful consequences associated with exposure to healthcare.[28]

Malpractice Litigation and For-Profit Healthcare

As an indicator of poor quality, medical malpractice litigation is viewed by others as a driving force for the defense of over utilization of services, leading to increased spending and exposure to unnecessary risk for the patient.[29] Malpractice litigation might also inhibit error disclosure and be counterproductive to efforts to improve quality. Findings from a review of 37 studies in 2020 found no association between measures of malpractice liability risk and healthcare quality and outcomes.[30] The authors concluded that malpractice liability risk might not be an effective deterrent in preventing substandard care.

Additionally, the increase in for-profit healthcare delivery systems, specialty ("boutique") hospitals, and increased office-based

surgery is a concern for some regarding cost and waste in the system. There is a fear that such practice modes "skim" the most profitable segment of income from the traditional hospitals, leaving the larger nonprofit and public entities at risk for financial ruin. There is also a potential conflict of interest when the providers are stakeholders in these healthcare entities. However, a cross-sectional study of 31 provider-led health plans (PLHPs) reported higher Medicare Advantage program star ratings, effectiveness, access, and patient satisfaction among PLHPs compared with non-PLHPs, and lower procedure rates.[31] The association between PLHPs and outcomes did differ by plan size, nonprofit status, and region. This heterogeneity is likely attributed to multiple factors, including population needs, enrollment policies, and leveraging of health system resources.

Politics and the National Pain Strategy

Finally, the politicization of decisions affecting healthcare through the expanding role of government and big business in scrutinizing and regulating its practice is a huge force impacting quality and cost.[32] Examples include potential implications of United States Supreme Court appointments, political influence from industry campaign donations that influence decision makers on a range of issues, including coverage for new technology, payment levels for a care sector, interpretation of a Medicaid regulation, classification of a hospital as "rural" or "critical access," measurement and reporting of quality, or even coverage for physician counseling on end-of-life care options. The toxicity of politics perpetuates enormous waste.

In 2010 the National Institutes of Health (NIH) contracted with the IOM to make recommendations to increase the recognition of pain as a significant public health problem. In response to the final report,[33] the Department of Health and Human Services asked the Interagency Pain Research Coordinating Committee to oversee the creation of a National Pain Strategy (NPS). Evidence from this report suggests that wide variations in clinical practice, inadequate tailoring of pain therapies to individuals, and reliance on relatively ineffective and potentially high risk treatments such as inappropriate prescribing of opioid analgesics or certain surgical interventions that contribute to poor quality care for people with pain and increase healthcare costs.[34] The NPS aligns with the triple aim and recommends improvements in standard methods and metrics that can reveal the pattern of health services, including over and under treatment, costs, and quality of care. The NPS provides a roadmap with substantial broad and specific political implications, including concrete steps to transform pain education, models of care, and payment structures. However, transitions in political power, available data and funding, and the opioid epidemic continue to impact implementation progress.[35]

What Is "Quality" in Pain Management?

Few explicit definitions of quality pain management can be found in the literature. This is partly because, in the history of medicine, views on pain have only relatively recently changed from that of a mere symptom to a field of study and practice specialty. As well, definitions of quality have historically been couched in quality assurance (QA) paradigms popular in the 1970s and 80s that relied mainly on inspection and audit activities aimed at identifying and isolating performance problems. In QA, standards of care are used as yardsticks, focused on identifying adverse outcomes, reducing providers' errors in the care of individual patients, and censuring responsible parties. The difficulty with the QA model is that feedback comes too late in the process and does little to explain differences in practice or outcomes. Also, medical records, a primary source of this type of quality review data, are notoriously incomplete and are often missing information important to evaluate the quality of pain management. In 1990, Mitchell Max, then chairman of the American Pain Society's (APS) Quality of Care Committee, suggested that the traditional formula of QA and education was insufficient to improve pain management and treatment outcomes.[36] Citing the failure of these efforts to change practice, Max suggested that a series of background factors must be addressed in the context of the clinical setting bringing attention to QI in the field of pain management.

In 1996, Sanders and colleagues forwarded guidelines for a uniform approach to a quality assessment of programs that treat persons with chronic non-cancer pain syndromes hinting at a definition of chronic pain care quality.[37] The guidelines were meant to be used as a complimentary document to those published by the CARF and to evaluate interdisciplinary chronic pain programs based on eight basic outcomes objectives including:

1. Reduction in the misuse of medications (if present)
2. Increase in physical function
3. Increase in productive activity at home, socially, and/or at work
4. Improvement in overall mood
5. Reduction in patients' subjective pain intensity
6. Reduction in use of and expenditures for healthcare
7. Where applicable, achievement of case settlement
8. Minimizing pain treatment program costs without compromising the quality of care.

Given the evolution of the healthcare system, frequent updates were recommended, but to date, there have been no visible coordinated efforts to further specify quality definitions for chronic pain programs until the development of the NPS.[34]

Under the leadership of Max, the APS provided QI guidelines for acute and cancer pain.[38] The recommendations specify that all care settings formulate structured, multilevel systems approaches that are sensitive to the type of pain, population served and setting of care that ensure prompt recognition and treatment of pain, involvement of patients and families in the pain treatment plan, improved treatment patterns, regular reassessment and adjustment of the pain management plan as needed, and measurement of processes and outcomes of pain management. This work helped shaped one explicit definition of quality pain management to include appropriate assessment (screening for the presence of pain, completion of a comprehensive initial evaluation when pain is present, and frequent reassessment of patient response to treatment); interdisciplinary, collaborative care planning that includes patient input; appropriate treatment that is efficacious, cost conscious, culturally and developmentally appropriate, and safe; and access to specialty care as needed.[39] A more recent concept evaluation of quality pain management in adult hospitalized patients concluded that pain management quality is a multidimensional concept that encompasses several subconcepts (Box 6.1), and valid, reliable, and operational measures of structure, process, and outcomes are needed.[40]

Quality Assessment and Measurement

Demand for measurement of healthcare quality continues to grow from all fronts, including managed care plans, healthcare consumers, accreditors, and clinicians. The national quality forum (NQF)

• BOX 6.1 Characteristics of Quality Pain Management According to the Donabedian Model[40]

Structure

- system-wide efforts and organizational commitment
- policies and standards supportive of effective pain management
- monitoring effectiveness and appropriateness of pain management
- staff education and training
- interprofessional care
- competent staff
- access to specialized care
- accountability

Process

- prompt recognition of pain
- screening, standardized assessment, and reassessment of pain, based on self-report
- documentation of pain assessment
- appropriate, safe, individualized, evidence-based pain treatment
- patient and family education
- identification of patient groups at risk for inadequate pain treatment
- patient participation
- caring attitude and trust in patient/provider relationship
- continuity of care

Outcomes

- reduced pain severity
- acceptable pain relief
- minimal pain interference on physical and psychosocial function, and quality of life
- minimal suffering from pain
- minimal side effects/adverse effects from treatment
- satisfaction with pain management

was created in 1999 by a coalition of public and private sector healthcare leaders with representatives from providers, purchasers, and consumers as well as the agency for healthcare research and quality (AHRQ), the Centers for Disease Control and Prevention (CDC), the Centers for Medicare & Medicaid Services (CMS), and the Health Resources and Services Administration.[41] Under legislated authority, the NQF-convened Measure Applications Partnership advises the federal government and private sector payers on the optimal measures for use in specific payment and accountability programs. There are five major hospital quality measurement sets endorsed by the NQF,[42] that were developed for a variety of purposes, including QI, pay for performance, and public health monitoring, including:

1. AHRQ Quality Indicators
2. National Hospital Quality Measures
3. Consumer Assessment of Healthcare Providers and Systems Hospital Survey
4. TJC's performance initiative ORYX®
5. Leapfrog Group's Measures

These measurement sets focus on quality and safety and utilize administrative data, patient medical records, and patient surveys.

Recognition of the differences in measures for performance (accountability), research, and QI is important because the **measurement is not a neutral activity, meaning there can be unintended consequences. One example being attempts to quantify pain using the** zero to ten **scale combined with the infamous campaign to make pain a "**fifth **vital sign" that contributed to the overprescribing of opioids.**[43]

Performance Measures

Accountability measures are performance indicators used by purchasers of healthcare to compare services. Performance indicators are typically public and intended to measure variations and improvements in performance and reflect the concerns of patients, providers, regulators, accreditation bodies, and other stakeholders. These indicators are often rate-based and reported as fractions or percentages of a total number of eligible events. The theory is that performance measures create competition in the marketplace, which will lead to improvements in healthcare quality and service. However, **success in improving quality and safety through the use of public performance reports has been mixed.**[44–46] **This is** partly because of **the choice of comparison measures with insufficient evidence of validity and how the measures are used. Measures should be carefully chosen for attributes (Box 6.2) that make them appropriate for the purpose used and support the intended goal.**[47,48] **Use of poorly designed measures may lead to misinterpretation of findings.**

The use of performance measures and the report cards that derive from them to rate institutional, practice, and individual physician performance continues to grow and be tied to payment models. Financial incentives to reward performance measures

• BOX 6.2 National Quality Forum (NQF) Criteria for Evaluating Measures Suitable for Public Reporting[48]

- **Standardization**: The measures are standardized at the national level, which means that all healthcare providers will be reporting the same kind of data in the same way.
- **Comparability**: If appropriate, the results are adjusted for external factors that could make a healthcare organization's performance appear better or worse than it really is; such factors include age, education, gender, income, and health status.
- **Availability**: Data will be available for the majority of healthcare organizations that you are profiling.
- **Timeliness**: The results will be available in time for you to produce and distribute a report when it is most needed by consumers.
- **Relevance**: The measures address the concerns of your audience.
- **Validity**: The measures have been adequately tested to ensure that they consistently and accurately reflect the performance of healthcare organizations.
- **Experience**: Healthcare organizations have experience with these measures to be confident that the measure reflects actual performance and not shortcomings in information systems.
- **Stability**: The measures are not scheduled to be "retired," e.g. removed from a measurement data set to make room for better measures.
- **Evaluability**: The results can be evaluated as either better or worse than other results, in contrast to descriptive information that merely shows how healthcare organizations may be different from each other. For example, a complication rate is an evaluable measure because we know that a lower rate is always better; in contrast, a Caesarian-section rate is not evaluable because we do not necessarily know whether a higher rate or a lower rate is desirable.
- **Distinguishable**: The measures reveal significant differences among healthcare organizations.
- **Credibility**: The measures are either audited or do not require an audit.

include accountable care organizations and bundled payments, value-based purchasing, or pay-for-performance (P4P) programs. All are complex, with limited evidence from which to draw conclusions.[49] Participation has been somewhat voluntary, and the financial incentives have been either paltry, easily gained, or both. Regardless, legislation has accelerated a shift to value-based payments, as evidenced in 2015 when the Department of Health and Human Services announced their intent to tie 85% of all traditional Medicare payments to quality or value by 2016 and 90% by 2018.[50]

Physicians have been reported to support the use of evidence-based measures that are congruent with provider expectations for clinical quality, targeting areas of poor performance and de-emphasizing areas that have achieved high performance.[51] Thus measures targeting process-of-care or clinical outcomes that are evidence-based and viewed as clinically important may inspire more positive change than programs using measures targeted to efficiency or productivity or those that do not explicitly engage providers from the outset. As mentioned, a challenge is that the correlation between process measures that tend to be those most easily measured, and outcome measures that are more difficult to measure, remains controversial. In addition, the use of composite indicators that combine performance measures presents challenges to interpretation distortions and the ability to guide improvement efforts.[52]

Research Measures

In contrast to performance measures, the purpose of measurement for research on quality is to generate new knowledge, though often with limited generalizability. Research on quality may focus on methods of implementation for new processes or outcomes. Measurement for research requires control of all possible variables, yet the study of quality of care must often rely on pragmatic and hybrid study designs because of the complexity of the interventions and context of the clinical arena.

Quality outcomes research has resulted in new measures of quality to help improve clinical practice, especially in the treatment of chronic illnesses such as back pain, where improved function is a primary objective.[53,54] Methods required for selecting or developing a psychometrically validated measure for quality research are beyond the scope of this chapter. Much has been written about the validity and reliability of the current pool of clinical outcome measures, including debate about use as a reference standard in responsiveness studies or as an accurate overall assessment of change. Greater consistency is needed in research measures, hence the development of the NIH Pain Consortium PROMIS® (patient reported outcomes measurement information system), a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children.[55] Drawing heavily on the PROMIS methodology, the NIH pain consortium has developed research standards for chronic low back pain, including recommendations for definitions, a minimum dataset, reporting outcomes, and future research.[54]

Quality Improvement (QI) Measures

Measurement for QI is intended to understand a process, the attitudes of key process workers and customers, and to motivate all relevant personnel to improve and to evaluate changes that have been made. Measures chosen for QI must be few and easy to collect because there are often limited resources and time to collect them. Measurements should be made over a short period so that data can be collected periodically and, most importantly, be available to provide timely insight into a problem. A criticism of QI has been the lack of rigor in the methodologies used to generate data with resultant doubts about the validity and reliability of QI measures.[56] However, there are no gold standard methodologic approaches to QI measurement development. A more thorough description of QI approaches follows.

Continuous Quality Improvement (CQI) or Total Quality Management Approaches

Used for years in the manufacturing industry, QI is a compilation of methods adapted from psychology, statistics, and operations research to avert predictable human errors, eliminate unnecessary and harmful variations in practice, and improve the production of goods and services.[57] Of note, many assessment techniques developed in engineering and used in QI (e.g. statistical process control, time series analysis) have more power to inform about processes and context than randomized controlled trials.[57] Continuous QI (CQI) is a philosophy and involves enlisting an entire organization to work toward a goal of continuous improvement in quality by carefully studying the process one is attempting to improve and changes the responsibilities and power of frontline workers. There are numerous approaches to QI, but the general principles are similar.[58] All focus on reducing unnecessary variation in production processes, standardization, and continuous improvement in outcomes rather than on the identification and elimination of "defects." The following four major frameworks for CQI share the philosophy that quality problems are process problems rather than people problems and base decisions on data, not hunches or opinions.

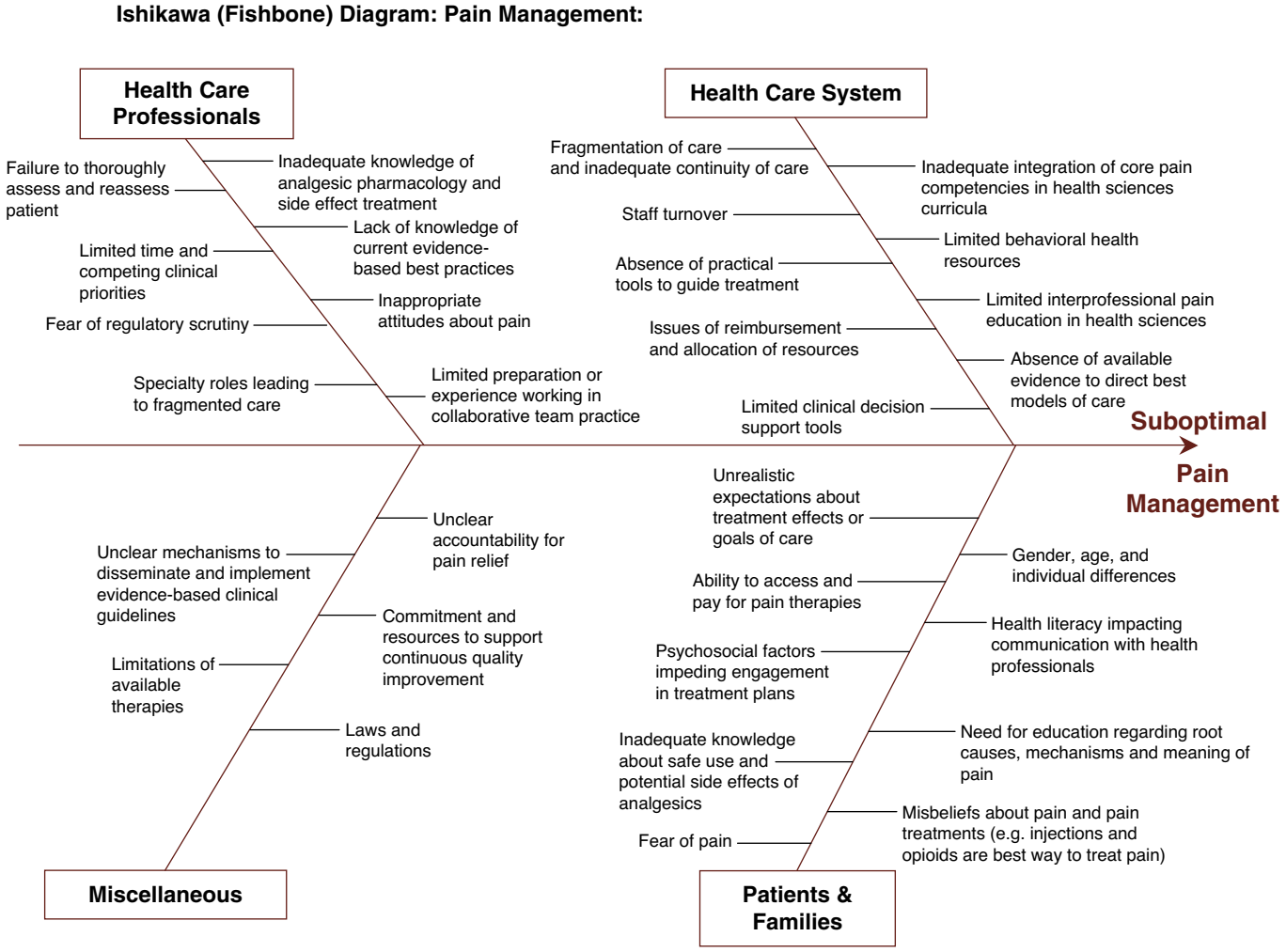
1. **The PDSA approach** (an acronym that stands for Plan, Do, Study, and Act) was first popularized by Edwards Deming (1900 to 1993), an electrical engineer, and is a rephrasing of the scientific method.[59] This method is driven by three primary questions: (1) what are we trying to accomplish, (2) how will we know that a change is an improvement, and (3) what changes can we make that will result in improvement. Continual improvement is made through repetitive iterations of the PDSA cycle. Deming is also known for his "profound system of knowledge,"[60] composed of four interrelated parts:
   1. Appreciation for a system
   2. Understanding variation
   3. Theory of knowledge or how people's view of what is meaningful impacts their learning and decision making
   4. Psychology

   Deming's work was influenced by Walter A. Shewhart, a physicist known for his developments in using statistics such as upper and lower control limits set at three standard errors above and below the mean to identify major causes of variation.
2. **Total Quality Management (TQM)**, attributed to Joseph M. Juran (1904 to 2008), builds on the work of Deming to prioritize customer expectations and team-based approaches to improve products and customer satisfaction.[61] Juran is attributed with the development of the Pareto principle (the 80-20 rule), which states that 80% of the effects in a system arise from 20% of the causes. TQM integrates all employees into the common goal of QI. Adapted by the IHI, team-based improvements are accomplished by using analytical

tools (e.g. flowcharts, statistical charts) and process techniques (e.g. brainstorming, nominal groups, consensus decision making).

3. **Six Sigma** is a management system developed by Motorola in 1986 to reduce variability within work processes by reducing error rates.[62] A five step methodology known as DMAIC (define, measure, analyze, improve, control) is followed using histograms, run charts and Pareto charts, and Ishikawa or "fishbone diagrams" most relevant to the variables to be addressed by the QI team. An example of a pain management fishbone diagram can be seen in Figure 6.1.
4. Finally, **Lean** emerged from the Toyota Production System in the 1990s and is aimed at reducing waste or non-value-adding activities. Value stream mapping[63] is used to visualize materials and information in a process and identify excess steps and bottlenecks such as wait times, motion, and cost of quality. Value stream mapping helps analyze the current state and design a future state for the series of events that take a product or service from the beginning of the specific process until it reaches the customer.

TJC has constructed a framework utilizing Lean and Six Sigma methods along with a systematic approach to change management to help healthcare organizations create a culture of high reliability for quality and safety.[64] Medical students from the Columbia-Bassett Medical School used a Lean Six Sigma approach to pain management when Hospital Consumer Assessment of Healthcare Providers and Systems survey data revealed opportunities for improvement.[65] Analysis of patient survey data revealed timeliness of addressing pain and feeling the care team understood their pain significantly correlated with being "very satisfied." These two variables were identified in a Pareto analysis as accounting for 71% of defects. Process mapping helped identify root causes, and a successful procedure was created to focus on response time for pain-related calls from patient call to nursing contact.



• **Figure 6.1** Ishikawa (Fishbone) Diagram: Pain management example
Also called a cause-and-effect diagram, the Ishikawa or fishbone diagram helps staff track down the reasons for imperfections, variations, defects, or failures. This tool can be useful when identifying possible causes for a problem. The diagram looks just like a fish's skeleton with the problem at its head and the causes for the problem feeding into the spine. Brainstorm all the possible causes of the problem. Ask, "why does this happen?" Consider all major categories of causes of the problem or use generic headings: methods; machines (equipment); people (manpower); materials; measurement; environment. As each idea from a person is given, writes it as a branch from the appropriate category. Causes can be written in several places if they relate to several categories. Continue to ask "why?" and generate deeper levels of causes. Layers of branches indicate causal relationships.

Though the evidence supporting these CQI methodologies in healthcare is positive, it remains limited and may only have modest effects on outcomes at best.[66]

Reducing Unnecessary Variation by Understanding Root Cause Analysis

The process of reducing variation or eliminating misuse, underuse, or overuse of treatments is inherent in the standards of evidence-based medicine. It is important to recognize that variation may be good or bad, or neither. It may indicate significant overuse or underuse of a therapy and thereby signal that either the science of the therapy is poor or that it is being applied haphazardly. However, before practice data can truly be defined as significant variation, it must be assayed for any underlying reasons. This includes exploring potential root causes and associations of multiple factors influencing diverse practices, such as dissimilarities in supply and demand because of geographic economics and climate. For instance, findings in the variation of inappropriate use of MRI for occupational low back pain showed significant associations based on gender, state workman's compensation policy not limiting initial treating provider choice, higher state orthopedic surgeon density, and lower state MRI facility density.[67] The reader is reminded that associations are not causation. In reality, a deeper inquiry into actual root causes is needed focusing on systems and processes in an organization to identify potential targets for improvements.

Statistical control charts are often used to determine if a variation is because of chance or special causes. Common-cause variation is chance or random variation where no one or combination of factors is affecting the process variation, whereas special-cause variation is when one or more factors influence the process variation in a non-random way. Five root cause analysis tools (Box 6.3) are commonly used in QI efforts, each appropriate for different situations.[68–70] The value in finding variation in care is to provide a signal that there may be best practices that can be emulated, but best practices can only be determined if variation is understood. Again, not all variation is misuse, overuse, or underuse.

Implementation Science and Toolkits

Because simply becoming aware of or being educated about the need to improve quality rarely produces the type of behavior changes required, more is needed. Improvement science overlaps with implementation science and other commonly used terms (e.g. translational research, knowledge transfer) to refer to dissemination and implementation strategies for new knowledge or information.[71] All use the scientific approach to systematize changes using social sciences to provide a conceptual and methodologic framework for the complexity of the phenomena at stake.[72,73] These methods have moved healthcare from more intuitive approaches to improve quality of care to the acknowledgment of the need for more planning and systematization with greater incorporation of the social sciences and enhancement of the role of context.[74] Improvement science identifies the intervention's technical component, the implementation strategy, and the context within which the intervention is implemented. Critical contextual factors include the impetus for change, leadership commitment to quality, professionals' engagement in problem solving, organizational alignment of objectives, resource allocation and action at all levels of the organization, and overcoming barriers.[75] Though the task may seem overwhelming, it merely emphasizes the need for teamwork, planning, and appreciation for the interrelated parts of the system.

To aid individuals with a practical approach to implement systematic changes, toolkits have been developed to address several topics, including pain management with reports of positive effects on clinical processes. However, robust research is needed.[76] Toolkits typically include introductory and implementation materials (e.g. research summaries), healthcare provider tools (e.g. care plans), and materials for patients. The American Academy of Family Physicians has a toolkit designed to help family physicians identify gaps in practice flow,[77] standardize evaluation and treatment of chronic pain patients, and facilitate conversations surrounding pain and treatment goals, as well as identify and mitigate risk. It contains primary care, patient centered resources that highlight key workflow features to streamline delivery and offer best-care medicine. The Veteran's Health Administration designed a tool as part of its NPS to assist healthcare providers and facilities to devise methods and implement processes to measure pain treatment outcomes based on focus (patient or process), type of pain (acute, chronic, or pain at end of life), and practice setting.[78] As well, the Society of Hospital Medicine (SHM) has produced an implementation guide[79] to provide practical advice to hospitalist physicians and other leaders who are developing programs to improve pain management in their services and facilities. The focus is on medical patients, though many of the principles described are relevant to patients recovering from surgical care who are increasingly co-managed by hospitalists.

Benefits and Steps in Constructing a CQI Program for a Pain Practice

There are several ways that a CQI program can help a pain practice, including the approbation of accreditors and P4P programs that tie some portion of provider income to either process or outcome achievements. Additionally, benchmarking to elucidate best practices can add value to the community through sharing lessons learned in the "real world" of clinical practice with others in the form of scholarly projects.[80–83]

CQI programs may improve pain treatment quality by simply inducing a more extensive review of a patient's history. For instance, inquiry about patient risk adjustors may lead to the recognition of mental health issues that could significantly affect the outcomes of any pain treatment plan. The use of baseline patient measures can direct care and provide an understanding of the likely potential for meaningful improvement in function and pain severity by identifying risk factors for long term treatment failure. Studies with longitudinal designs of persons with chronic pain indicate associations between measures of baseline self-efficacy and pain severity, functional impairment, and affective distress at follow up, as well as potential moderating effects of sociodemographic characteristics.[84] Considerations for risk adjustment also come into play when measuring opioid utilization and risk of opioid use disorder; for example, geographic epidemiologic work demonstrates variations in opioid-related overdoses that are presumed to be related to differences in opportunities and resources at the United States county level, which include rates of disability, employment, housing crowding, insurance, and racial and ethnic diversity.[85]

The use of a clinical database for monitoring patient outcomes provides a sense of participation in the process for the staff whose work is being assessed, a key factor in their acceptance and

• BOX 6.3 Common Root Cause Analysis Tools[69,70]

1. Pareto Chart

A Pareto chart is a histogram or bar chart combined with a line graph that groups the frequency or cost of different problems to show their relative significance. The bars show frequency in descending order, while the line shows cumulative percentage or total as you move from left to right.

Hypothetical example

2. 5 Whys

This method uses a series of questions to examine and peel away surface layers of a problem to get to the root cause. Each time you ask why the answer becomes the basis of the next why. This tool is most useful for problems where advanced statistics are not needed. A deeper analysis may incorporate the results of a Pareto analysis. It may take more than five times to uncover the problem.

For example

- *Why is the patient not seeing the right provider in a multidisciplinary pain clinic?* According to a Pareto chart of contributing causes, the biggest factor is the scheduling center's routine to calendar a patient for the earliest available appointment.
- *Why does the call center schedule for earliest available appointments?* Because they have no triage or screening criteria or information to do otherwise.
- *Why is there no triage or screening criteria?* Because the pain clinic has not created triage criteria that can easily be used by a scheduler.
- *Why hasn't the clinic created triage criteria?* Because historically, the workflow involved a nurse triage of incoming referrals.
- *Why is the nurse triage no longer happening?* **Because the need to clarify triage criteria with the appointment scheduler was not captured in a reorganization of the pain clinic and change in nursing roles.**

3. Fishbone Diagram (see Fig. 6.1)

Also called an Ishakawa or "cause-and-effect" diagram, a fishbone sorts the possible causes into various categories that branch off from the original problem. Multiple sub-causes branch off each identified category.

4. Scatter Plot Diagram

A scatter diagram plots your suspected cause (or independent variable) on the x-axis and the effect (or your dependent variable) on the y-axis. This scatter plot or diagram helps uncover relationships. If the patterns show a clear line or curve, you know the variables are correlated and can proceed to correlation or regression analysis.

Legend: Correlation between RMDQ scores and pain intensity. Scatter plot showing the relationship between disability (RMDQ scores) and pain intensity scores measured with visual analog scale. The many small circles represent the plotted values obtained for each of the variables, while the line represents the best fit for the correlation between them.

RMDQ = Roland Morris Disability Questionnaire

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Scatter Plot Source[70]

Doualla M, Aminde J, Aminde LN, et al. Factors influencing disability in patients with chronic low back pain attending a tertiary hospital in sub-Saharan Africa. *BMC Musculoskelet Disor.* 2019;29(1):25.

5. FMEA

This is a proactive assessment tool and qualitative analysis method used during the process or product planning to identify potential systematic failures, consequences, and causes before events occur. The FMEA process focuses on causes and opportunities for preventing negative effects and involves scoring for severity, occurrence, and detection ratings that allow calculation of a risk priority number to determine further action.

Potential FMEA [system, product or process]

Background				Rating				Countermeasure			Results			
Description of Process	Potential Failure Mode	Potential Effect(s) of Failure	Potential Root Causes	SEV	OCC	DET	RPN	Owner	Due	Recommended Actions	SEV	OCC	DET	RPN

SEV = severity (1-10), OCC = occurrence (1-10), DET = detection (1-10), RPN = risk priority number

enthusiasm for the benefits of CQI. An active CQI program will also allow practitioners to evaluate the effects of introducing new therapies or treatment algorithms into their practices and either prove or disprove their value.[86]

The most significant hurdle in CQI for pain practices is a lack of apparent benchmarks or national "best practices" that providers emulate. Using the literature to establish benchmarks is prone to error because of the significant positive bias in the reporting of the success of techniques there. Overall, the evidence is not clear as to which, if any, interventions improve many chronic pain states.[87,88] The analysis of practice patterns among either partners or an unassociated local group of pain practitioners is a potential source of evidence in those situations where there is a lack of randomized controlled trials in the peer-reviewed literature. Assessment programs under the mantel of "peer review" statutes will allow participating pain practices more timely and open means of sharing their own best practices to attempt to increase the quality of the community's pain care.

Creating a CQI Program for a Pain Practice

There are several steps in creating a CQI program for pain:

1. Identify and engage front line practitioners (physicians, nurses, therapists, case managers) who will be involved.
2. Gather those caregivers together to align their information goals and to craft a set of measures toward which all can agree that the program should be directed. A good starting point is the list put forth by the IOM's *Crossing the Quality Chasm* IOM,[89] with six specific targets for improvement:[89]
   a. Care should be *safe*.
   b. Care should be *effective* and based on proven *evidence and science*.
   c. Care should be *efficient* and *cost effective with no waste*.
   d. Care should be *timely*, with no waits or delays.
   e. Care should be *patient centered*: respect patient preference and give the patient control.
   f. Care should be *equitable* with no unequal treatment.
3. Pick outcome measures that will allow accurate assessment of the problem. Any evaluation of the overall quality of care needs to consider a patient's perception of quality and understand it is a cumulative process that develops over time, as the different attributes of the services available and their outcomes are revealed.[90] Indicators are of three types:
   a. *Structure measures* assess the characteristics of the practice or a facility, such as staff-to-patient ratios, presence of evidence-based policies, or continuing education supports. Structure measures may simply be the absence or presence of system supports but can be used to prioritize limited resources and standardize that which can be standardized.
   b. *Process measures* assess how care is provided in the practice. For instance, documentation and communication of critical steps in the workflow surrounding referrals and billing. The disadvantage to process measures is primarily in determining a link with the outcome. These must be considered surrogates for outcome in the many situations in which direct measurement of the outcomes is impeded by difficulty with risk adjustment or other barriers. Another limitation is that process measures are frequently used because they are relatively easy to measure, but they may have little connection to true clinical outcomes. An example is how long it takes for a patient to be roomed after arrival.
   c. *Clinical outcome measures* include using repeated patient health status testing to determine health status longitudinally after interventions. In most practices, it would be expected that some sort of evaluation of patients in this regard would be collated and sorted by diagnosis, demographics, and intervention. This is a critical step to monitor for overuse or underuse of medical therapies.
4. The chosen measures should have the following characteristics:[91,92]
   a. *Relevance*. They should directly relate to the goals of the group, and it should be true that the interventions of the group have an effect upon them.
   b. *Timeliness*. The measures should be collected in a timely manner to relate them as closely as possible to the interventions that the practitioners wish to assess.
   c. *Reliability*. The measures should be accurate and consistent no matter when or who is assessing and recording them.
   d. *Validity*. The valid measure is sensitive to changes that the practitioner can effect.
   e. *Precision*. The measures should be clearly defined and leave little potential for individual or erroneous interpretation.
   f. *Cost effectiveness*. A CQI program costs money, and the measures should be significant enough to your patients and your practice that they are worth the time and money expended on the process of collection and analysis.
   g. *Provider control*. The variable measured must be one that the provider or organization can control, or it is not worth measuring. For instance, measuring patient self-reported pain levels one year after intervention for a chronic pain condition is unlikely to reflect a process that the provider can control because of the impact of the intervening healthcare and patient activity over the course of one year.
   h. *Clear meaning*. The measure must be one that is easily understood by all concerned.
5. Terminology-once the practitioners have chosen the measures. The terms may need to be adjusted to be in congruence with standard nomenclature. The accepted standard is a somewhat moving target, but SNOMED-CT (systemized nomenclature of medicine-clinical terms) is the designated unified medical language systems by the NIH and National Library of Medicine (NLM) to promote the creation of more effective and interoperability between computer systems, including electronic health records in the United States. Thus all practitioners should make sure their own terms are "cross-walked" to SNOMED terms so that they report data that, where possible standardized for accreditation and certification bodies and payers. One can download all of SNOMED at the NLM site, which has licensed SNOMED for use by any entity within the United States. This site is www.nlm.nih.gov/research/umls, but the data sets are raw, and most practitioners would need help manipulating them. This crosswalk process may be accomplished by several vendors.
6. *Risk adjustment* must be included in the design of the monitoring system for the measurements to have any utility for identifying high quality and best practice. Risk adjustment uses multivariate regression methods to measure performance by removing between-clinic differences associated with factors outside of a clinic's control and constructs a measure that reflect a clinic having comparable patients. Risk adjustment is still a confounding science, with many controversies but has been used for several purposes, including prediction of concurrent and future healthcare utilization levels of insured patients who receive some care from complementary and alternative medicine providers compared with those who receive care only from conventional practitioners to provide spine surgeons and hospitals a basis to make informed decisions for elective single-level posterior lumbar spine fusions.[93,94]

The vagaries of risk adjustment recommend that practitioners use tools of measurement that are already validated. If a pain practitioner or group decides to create a completely new measure, careful attention to risk adjustment theory and its evaluation in the literature or appropriate texts is recommended.[95] Risk adjustment in chronic pain practice poses very significant challenges, in view of the diversity in the types of adjustors that are operant in the widely diverse population of persons with chronic pain conditions, including multiple comorbid conditions ranging among physical disabilities, economic and social burdens, and mental health disorders. Nonetheless, small groups of clinical experts can choose risk adjustment indices with validity if the process is done with bias controls and if there is the involvement of biostatisticians and epidemiologists. The use of a standardized pain classification is important. For instance, the analgesic, anesthetic, and addiction clinical trial translations, innovations, opportunities, and networks

(ACTTION)-APS Pain Taxonomy (AAPT) reflects common features and comorbidities, including psychosocial factors that influence the diagnosis and trajectory of chronic pain disorders.[96]

Use of Outcome Measurement Tools for your Pain Practice CQI Program

Validated quality of life or condition-specific assessment tools used in clinical practice (e.g. EQ-5D-5L, SF-12 or 36 measures, Roland Morris back pain, Waddell disability index, the fibromyalgia impact questionnaire, others) might be considered for a pain CQI program.[97–99] These have been used in scientific studies to measure some of the variables that would be valuable to a pain program. However, the reader is cautioned that a great deal of variation exists in the versions of some of these instruments published in the literature.

Gathering data is ideally managed in part by using patient surveys before and after the provision of services, with timing appropriate to the nature of the patient's condition and the expected effective duration of the intervention. The use of both a short general health assessment and a specific pain evaluation tool are probably the most basic approach. Reviews of the relative merits of acute and chronic pain measurement tools advocate well for certain tools in certain patients or for certain conditions.[100] Brevity and speed of both information entry (either by the patient or staff) and data analysis are salutatory aspects of an outcome measurement system, and these should all be considered in determining which instruments will be used.

The desire for universal measures of self-reported health, including the ability to compare disease burden and treatment impact across various chronic conditions, and to be able to measure patient-relevant outcomes, using a common metric, with people who have more than one disease or medical condition led to the development of NIH PROMIS measures.[101] The current body of clinical validity evidence for the nine PROMIS measures (self-report measures for adults for functions, symptoms, behaviors, and feelings) indicates that they too are effective across a range of chronic conditions,[102] though the practicality of using in clinical practice is debatable. Using computerized surveys that leverage item response theory (e.g. in the waiting room or online prior to a clinic visit) holds the potential to reduce staff and patient burden and improve data integrity by maximizing accuracy.[103]

One important issue is the significance of any change observed in the various measures over time in each patient. Some of the recommended tools were developed primarily to look at patient cohorts rather than for point-of-care decision making with individual patients. This area of research is still emerging, and the reader is encouraged to monitor the literature closely to help be sure that his or her use of the tools is valid.

Standard Nomenclature and Pain Registries

Many organizations are still attempting to codify and make uniform the "dictionary" of terms that are used in quality databases. A source of guidance in this endeavor is the document from the American Society of Anesthesiologists (ASA) titled "Guiding Principles for Management of Performance Measures by the American Society of Anesthesiologists," available on the ASA website www.asahq.org. Several organizations are involved in the effort to codify terminology in addition to the ASA, including the Anesthesia Patient Safety Foundation (APSF) and its Data Dictionary Taskforce, and international groups such as the World Health Organization (WHO). The number of societies, the importance of the task, and the lack of certainty in the area means that any database will be mutable over time. The benefit of such malleability of design, which will always cost money, is that the practitioners who use it will be better assured that they will be in compliance with the requirements of the accreditation agencies (e.g. TJC, Accreditation Association for Ambulatory Healthcare (AAAHC), and others), which will also be set and amended in the years to come.

Active learning is critical to continuous improvement and requires a means of quickly harvesting internal and external best practices and creating multiple feedback loops.[104] Utilizing communities of practice across the health system encourage participation in shared learning. While many still strive to implement CQI in individual pain management practices, Stanford has taken this a step further by aggregating data in the form of a national pain registry that can be utilized for QI purposes in a "real world" clinic setting. The Collaborative Health Outcomes Information Registry (CHOIR) is an example of a learning health system developed to collect information on pain patients and the effectiveness of therapies.[105] CHOIR is an open source, open standard, free, secure, electronic, learning health system designed to capture detailed, longitudinal patient reported outcomes data on physical, psychological, and social health. CHOIR was developed to inform point-of-care decision making, provide software-based decision making, and act as a platform for comparative effectiveness research, longitudinal outcomes research, and practice-based evidence trials. CHOIR also integrates NIH PROMIS measures to capture 15-20 domains of physical, psychological, and social functioning.[106] This effort exemplifies the broader view that is required to improve patient care and facilitate the discovery of novel solutions for pain management. The registry is currently shared by numerous pain centers nationwide, and data has been used for formative evaluations that allow for distinction between intervention and implementation failure, by identifying at an early stage whether desired outcomes are being achieved and if they are not, using the formative evaluation data to develop or refine implementation strategies to improve implementation success, as needed.[106,107]

An example of a web-based information system used by hospitals for an acute postoperative pain quality database is the international QI registry project termed "PAIN OUT."[108] Patient reported outcome data is collected using the validated International Pain Outcomes Questionnaire (IPOQ)[109] along with other clinical data in a standardized way. Following input of data, hospitals receive online feedback and can compare their results with other participating hospitals to help identify deficits to direct improvement efforts. Initially funded by the European Commission's 7th Framework Programme (Grant Agreement no. 223590), participating hospitals have to pay a moderate annual fee for the services provided.

Such megadata systems exist in other forms online as not-for-profit and profitable entities that collect quality assessment data on behalf of providers. The practice generally has access to their individual data and its analysis, but the business essentially "owns" the collective database. This information can then be subject to countless analyses. Thus it is not only used by the provider to assess and improve the quality of care in their private clinic but can be pooled for research purposes. Comparative effectiveness between distant practices and longitudinal data analyses are examples of the many uses of web-based data collection programs like these.

Still, further, the incorporation of new technologies in pain assessment systems using smartphones or smartwatches continues to grow.[110] Studies have shown that pain "apps" are workable and well-liked by patients and healthcare professionals.[111] Patients

are already participating in studies using telephone-based health coaching sessions supported by an internet-based application and an accelerometry activity tracker that remotely reports to the provider and, by extension, to a registry.[112,113] This information will allow the provider to track a patient's progress, evaluate the ongoing treatment and gather data that can later contribute to evidence-based practice, and document accountable care.

Summary

This chapter separates patient safety and QI as independent sections. However, both must be considered when reviewing strategies to improve either of them. A primary objective in the delivery of quality pain care is to make pain management accessible, optimal, and personalized for all. Practitioners must be scrupulous in evaluating procedures and therapies with rigorous doubt, eliminating those that do not prove valuable compared to alternatives that may be more banal and less lucrative. This is hindered by many challenges, including the need for payment reform to foster coordinated interdisciplinary care, pain self-management programs, patient education, psychological counseling and complementary and integrative health approaches, and access to medications. However, individual pain practitioners can impact quality by fostering methods to improve pain assessment and delivery of integrated, multimodal, interdisciplinary care that is effective and safe.[34]

SECTION II–PATIENT SAFETY

To Err Is Human and the Prevention of Harm

Patient safety is, based on the WHO definition, "the absence of preventable harm to a patient during the process of healthcare."[114] Patient safety, with its fundamentals of collecting and analyzing events as well as prevention of adverse events in a confidential environment, has become an indispensable discipline and element of healthcare quality.[115] There is reasonable debate as to whether or not a specific patient may be safe and whether or not a specific error contributes to real morbidity.[116] However, the public, legislators, and payers are convinced that both patient safety and human error are significant problems in today's healthcare delivery system. The healthcare industry is now urged to create a "culture of safety" at all levels of practice, which will put in place processes that will eliminate or decrease the impact of human error. A significant hurdle to the effort to improve safety is that there is insufficient data to assess healthcare safety or even definite identification of uniformly valid indicators of safety in healthcare.[117] Therefore which solutions, which information, and which technology will be of value in improving patient safety are still disputable.

Standardized and reliable definitions are needed to measure harm accurately and evaluate the result of patient safety. First, a medical error has to be distinguished from an adverse event. There are two major types of errors: (1) errors of omission occur because of actions not taken and (2) errors of the commission occur because of the wrong action taken.[118] Medication errors are among the most common medical errors,[119] and events reported in TJC sentinel events database.[120] Most errors in patient care do not arise from an individual but from conflicting, incomplete, or suboptimal systems and have the potential of being harmful.[121] An adverse event is a harmful injury resulting from a treatment and is not caused by the underlying medical problem and can be classified as preventable or non-preventable. These events, such as those associated with opioid treatment for chronic non-cancer pain, can be lethal, life-threatening, disabling, prolong hospital stay, and require additional monitoring.[122]

The publication of "to err is human" in 1999 was the IOM public alarm about patient safety and error in the healthcare delivery system.[123] The IOM recommended the creation of safety centers and organizations and motivated hospitals as well as professional societies to focus on patient safety. As an effect of the IOM, the government was one of the first to support safety research. Further, the 2005 Patient Safety and Quality Improvement Act stimulated the development of Patient Safety Organizations (PSO) and defined their role. The act called for a confidential culture of patient safety and for the establishment of a Network of Patient Safety Database to provide an interactive evidence-based management resource.[124] In the two decades since the IOM landmark report, additional areas of safety risk have been identified and targeted for intervention, such as outpatient care, diagnostic errors, and the use of health information technology.[125,126] Health information technology can improve patient safety, but its implementation and use have led to unintended consequences and new safety concerns (e.g. unavailable or malfunctioning hardware or software, failure to use health IT appropriately, alarm fatigue).[127]

The frequency of preventable harm remains high, and new scientific and policy approaches to address both prior and emerging risk areas continue to be needed. Based on different facets of patient safety and with varied scopes, several prominent groups have emerged:

1. **The WHO** launched the World Alliance for Patient Safety in 2004 in all member states to improve safety in healthcare.[128] Patient safety is not only a problem in industrialized countries but also a global problem. Prevention of healthcare-associated infections, hand hygiene, surgical safety, and patient engagement are targeted safety issues. The WHO emphasizes prevention, detection, and risk reduction through guideline implementation and establishment of a uniform classification of patient safety concepts, The WHO also aims to reduce iatrogenic harm from medications. Many patients may be exposed to risks from a combination of adverse reactions, polypharmacy, and miscommunication, and the WHO recommends national medication safety plans that focus on engaging patients and the public; medication as products; education, training, and monitoring of healthcare professionals; and systems and practices of medication management.[129]
2. **The AHRQ** has the federal lead in patient safety. It supports research of causes and the development of new strategies in patient safety, including integration within the healthcare industry. This center coordinates the PSOs and distributes knowledge about effective practices. The AHRQ offers the Patient Safety Network (PSNet),[124] a web-based resource of news on patient safety, as well as the Web M&M,[130] a morbidity and mortality round on the internet.
3. **The NQF** (discussed in part 1 of this chapter) helps improve the quality of healthcare in the United States by building, endorsing, and promoting national consensus about priorities, measurements, and their education. NQF oversees a patient safety measure portfolio and in 2017 endorsed new measures for the use of opioids from multiple providers and at high dosage in persons without cancer.[131]
4. **TJC,** advised by a panel of safety experts, has published national patient safety goals since 2002.[132] These goals are provided as clear, actionable statements, such as "use at least two patient identifiers when providing care, treatment, or services"

or "mark the procedure site," with the rationale behind these goals and the elements of performance. The main topics are identify patients correctly, improve staff communication, use medicines safely, prevent infection, identify patient safety risks, and prevent mistakes in surgery. Each year information is gathered about emerging patient safety issues to inform sentinel event alerts, standards and survey processes, performance measures, and educational materials.

5. **The IHI** is an independent non-profit organization founded in 1991. IHI initiated the 100,000 Lives Campaign (2004-2006), which was designed to save lives by introducing six safety problems in healthcare.[133] The campaign aims to reduce harm and deaths by the deployment of rapid response teams, evidence-based care for acute myocardial infarction, prevention of adverse drug events, central line and surgical site infections, and ventilator-associated pneumonia. The National Patient Safety Foundation (NPSF), initially created in 1997, merged with the IHI in 2017. The NPSF published *Free from Harm,*[134] 16 years after the IOM report, and called for a total systems approach to patient safety to replace piecemeal interventions. Challenges remain to address several major concepts for system-level action including[115]:
   - Medical education must be redesigned to prepare new physicians and other health professionals to function in these new safety cultures.
   - Care must be delivered by multi-disciplinary teams working in integrated care platforms.
   - Healthcare workers need to work in safe environments and find joy and meaning in their work.
   - Patients must become full partners in all aspects of designing and delivering healthcare.
   - Transparency must be a practiced value in everything we do.
6. **The Leapfrog Group** is a national nonprofit organization founded in 2000 by large employers and other purchases of healthcare.[135] They aim to reduce preventable medical mistakes, improve quality and affordability of healthcare and encourage healthcare providers to publish their quality and outcomes, and reward them for improving quality. This group focuses on four "leaps," including computerized physician order entry (CPOE), evidence-based hospital referral, ICU physician staffing, and a Leapfrog patient safety composite score that assesses a hospital's progress.[136]

Understanding the Components of Patient Safety

As the healthcare system has become more complex, communication breakdowns are common. Creating a culture where healthcare workers speak up candidly about concerns before problems occur is critical. TJC's sentinel event database identified communication as a leading root cause of sentinel events in the United States.[137] Past studies have indicated more than 65% of medical errors are caused by problems in interpersonal team communication citing seven categories of conversation that are especially difficult and at the same time essential for patient safety.[138] These include broken rules, mistakes, lack of support, incompetence, poor teamwork, disrespect, and micromanagement.

There is no single reason why a safety event happens. Instead, it is a combination of individual and system factors. This may include inattentive or carelessness leading to mistakes, procedural violations, or bearish behavior directly causing adverse events. The system can provoke an environment initializing errors based on organizational decisions, also called latent conditions.[139] While active errors are attributed to the immediate action of a human to cause an error, latent conditions allow active errors to occur, leading to an adverse event or harm to the patient. Latent conditions can be undetected for a long time before leading to a problem when combined with active failures. In creating safer processes, it is best to focus on system changes rather than on scrutiny of individual practitioner errors, as system errors are most causative of an adverse event.[140]

Culture of Safety and Safety Climate

The terms patient safety culture and climate are often used interchangeably in practice, but there are conceptually meaningful differences in their scope and depth. The notion of a patient safety culture originated from the experience in hazardous industries such as aviation and nuclear energy.[141] A safety culture depends on attitudes, beliefs, behaviors, perceptions, values, and practices shared by employees. Safety climate is the quantitative description or a way of measuring safety culture by taking a closer look at adverse events (outcomes measures), analyzing adherence to practices (process measures), or tuning of healthcare teams' attitudes about issues relevant to safety. Clinicians may feel that medical care is not amenable to the safety monitoring systems of other industries, yet emulation of highly reliable organizations within these other industries does lead to improvements in safety in healthcare.[142,143]

Across the globe, there are differences in the way that patient and occupational safety culture is perceived among different health professional groups, particularly between managers and bedside clinicians.[144] Healthcare providers define safety climate using three attributes: (1) creation of safe working environment by senior management in healthcare organizations; (2) shared perception of healthcare providers about safety of their work environment; and (3) the effective dissemination of safety information.[145] Evidence suggests that interventions such as team training, interdisciplinary rounding, or executive walk rounds can improve perceptions of safety culture and potentially reduce patient harm.[146]

The IOM not only proposed to build centers and organizations but also the creation of a culture of safety. Engaged senior leaders are important to an organization's successful development of a culture of safety. A just culture where providing safety-related information in a blame-free environment is rewarded, and people have the will and the knowledge to learn from mistakes (learning culture) are essential to develop a safety culture.[147] Teamwork and collaboration such as open communication have been defined as a second important behavior to support a culture of safety, especially considering the increasing complexity of today's patients.[148] As well, the use of standardized, evidence-based processes together with patient centered medicine has an important influence on patient safety culture.[149,150]

Strategies to Reduce and Improve Safety Events

Patient harm can be reduced in the same way engineers manage dynamic complexity as a system problem requiring interdisciplinary systems solutions.[151] Anticipating and preventing predictable risks and hazards through standard routines and protocols removes uncertainty, reduces information processing requirements, and, thereby, decreases possible memory lapses, judgment errors, or biases that can lead to adverse outcomes. Individual pain practitioners need to work together with others to understand the nature of the work, create detailed operating procedures and

contingency plans, and use the tools of science and technology (e.g. failure mode effects analyses, or hazard and operability studies) to shape the behavior of organizational members to avoid mishaps.

There is a retrospective (reactive) and a prospective (proactive) way to measure and improve safety. The retrospective way is the root cause analysis (RCA), described in part 1 of this chapter and commonly used in QI, error reporting systems, morbidity and mortality conferences, or malpractice claims. These methods seek to answer the question of what went wrong and why. We widely use these techniques to understand the causes of harm and to improve safety. A group of anesthesiologists from Seattle and Boston, for example investigated conditions and patterns in malpractice claims after interventional pain treatment at the level of the cervical spine. They found that injuries leading to malpractice claims were most often caused by direct needle trauma to the spinal cord; that these injuries were often severe, and they appeared more frequently in unresponsive patients.[152] RCAs increase the awareness of faulty processes and are more likely to detect latent errors and adverse events but bare the risk of spending resources on unnecessary interventions if not performed correctly or comprehensively. For example, errors in the use of patient controlled analgesia pumps or epidural line misconnections; remedial actions may be aimed at the wrong level of the healthcare system, such as education of individuals instead of innovations in pump or tubing connection designs.[153]

Though the strength of evidence may be low, a systematic review of varied interventions to promote patient safety in an inpatient environment reported several useful types of interventions such as team training and team communication tools, executive and interdisciplinary rounding, and the Comprehensive Unit-Based Safety Program (CUSP).[148] CUSP is a multifaceted strategy that pairs "adaptive intervention" use as a continuous learning strategy with technical interventions and application of best available evidence-based clinical care algorithms to improve patient safety and quality.[154] Adaptive intervention is based on the premise that systems can learn adaptively by reacting to a change in the environment and can learn by generating new knowledge and conditions.

Healthcare is continuing to organize for higher safety and reliability. Standardized protocols and checklists, pre-procedural and post-procedural briefings, incident reporting, and daily huddles all hold promise for enhancing safer care.[155] These types of activities are part of a comprehensive, organization-wide integrated approach to manage risk and to achieve safe and reliable performance, similar to the systems found in other industries. Checklists provide a means to translate evidence-based best practices to the bedside for a wide range of care processes. Well-constructed checklists codify interventions, remove ambiguity, and increase the reliability of care processes.[156] The American Society of Regional Anesthesia and Pain Medicine (ASRA) showed in a randomized simulation study that checklists improved not only medical management of local anesthetic systemic toxicity but also augmented non-technical performance.[157] Surgical safety checklists are widely used and associated with better postoperative outcomes, but this could reflect the wider quality of care in hospitals where checklists use is routine.[158] Clearly, no checklist has all the required interventions, and patients often require multiple checklists. Blindly following the rules can be deadly if it reduces the ability to adapt or react swiftly to surprises.

Failure Modes and Effects Analysis (FMEA)

FMEA is a proactive assessment tool and qualitative analysis method to identify potential systematic failures and their effects before events occur. The FMEA process focuses on causes and opportunities for preventing negative effects and involves scoring for severity, probability, and detection of failure reasons, as shown in Box 6.3. FMEA has been applied to assess risk with intrathecal drug (IT) delivery for pain management.[159] Human error, catheter issues, pump failure, and granuloma formation were considered severe safety concerns during IT therapy. Among 17 top failure modes, the methodology identified appropriate patient selection as the most critical component for the successful management of pain with IT therapy.

In 1974, Jick introduced a prospective concept based on trigger events.[160] Trigger tools such as the Global Trigger Tool is a form of medical record review often used as an adjunct to patient safety event reporting to reduce the number of adverse events that are undetected during hospitalization and primary care.[161] This tool seems more reliable than other methods to detect possible events, often discovering at least ten times more confirmed, serious events than other methods.[162] Searching for triggers typically associated with the most frequent and harmful adverse events allows for detection and measurement of "all-cause harm." This method has lower resource intensity through the use of sampling and has been shown to identify more than 90% of harm in hospitalized patients.[163] It is recommended that hospitals should report all adverse events as all-cause harm, meaning any event during the care process that results in harm to a patient, regardless of cause.[164] There is a strong relationship between all-cause harm and safety culture, employee engagement, and patient experience, indicating that when there is a positive patient safety culture, a more engaged employee, and a more satisfying patient experience, there may be less all-cause harm.[165]

Healthcare Education

Healthcare education has altered significantly over the years, with many professional societies adapting their curricula to focus on safety. The American College of Surgeons has integrated six core competencies defined by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Medical Specialties, which include listings of patient safety topics, teaching and learning strategies, and assessment methods. Learners and experts agree that topics within the domains of improvement science and nontechnical skills should be included in a formal curriculum.[166] Yet, there is wide variation on how well these topics are currently included in graduate medical education training programs. Since 2019, the ACGME also endorsed the disclosure of adverse treatment events as a common program requirement for resident education and experience. However, a survey of medical residents at the Yale Primary Care Residency Program endorsed the need for the design of a more specific and effective educational program.[167]

Professional education has not kept pace with increasing demands for collaboration-ready health workers in part because of disjointed and outdated curricula and a glaring mismatch of competencies to patient and population needs.[168] Interprofessional education is a growing trend across health professions and has been defined as when two or more professions learn with, from, and about each other to improve collaboration and the quality of care.[169] For interprofessional learning to occur, all three "with, from, and about" must be present. The Lancet Commission calls for education reform that is guided by the desired outcomes of transformative learning and interdependence in education.[168] Transformative learning has been called for in the field of pain medicine and involves fundamental shifts from fact memorization to the synthesis of information for decision making; from

seeking professional credentials to achieving core competencies for effective teamwork in health systems; and adaptation of global resources to address local priorities.[170]

Education is tightly linked with the introduction of new technologies. There are different ways to adopt new techniques and technologies into clinical use through education. Peyton's Four-Step Approach (1. trainer demonstrates, 2. talk the trainee through, 3. trainee talks trainer through, and 4. trainee does), and the traditional training model of "see one, do one" have both been shown to be effective though effects are variable.[171,172] Healthcare simulation can provide an opportunity to practice technical and nontechnical skills in a patient-safe environment, particularly the skills most required in dynamic and crisis situations. Simulation-based education is expensive, but it is cost effective if utilized properly and increases patient safety. Simulation-based training complements medical education in patient care settings but does not replace educational activities based on real patient care experiences.

In addition to simulation, several team training models and practical tools, and organizational interventions are available to help reach safety goals.[173] These include team strategies and tools to enhance performance and patient safety (TeamSTEPPS),[174] SBAR (situation, background, assessment, and recommendation) communication and patient handoff tool,[175] debriefing checklists, rounds, and redesigning structures to stimulate team processes and team functioning. Other important sources aimed at providing the evidence to improve patient safety and outcomes are clinical guidelines and practice advisories, like those published and steadily updated for regional anesthesia and pain medicine.[176] Based on current literature, expert opinion, and clinical data, these systematically formulated advisories aim to improve patient safety by reducing the incidence and severity of adverse outcomes in daily practice. These recommendations usually focus on clinical topics where treatment is as yet unclear. Consensus statements based on opinions today may be rewritten and changed when overruled by new scientific facts, and readers and writers are encouraged to continuously re-evaluate these recommendations.

Finally, in regard to education, patient centeredness is an essential element of quality and safety. Education and training programs should emphasize shared decision making with patients regarding realistic goals, expectations, and preferences to inform the pain care plan. Patients are uniquely positioned to provide important information potentially unavailable from other sources such as medical records and to engage in certain practices that may improve their safety. Interventions include patient and family education, encouraging patients to remind healthcare workers of safety practices such as hand washing, and to participate in reporting clinical errors. However, patient engagement is often low, and there is insufficient high quality evidence to exactly inform how to facilitate this in the clinical arena.[177]

Technology

The use of technology has facilitated many steps in patient care. The calculation of medication doses, imaging modalities, exchange of patient data between geographically or temporally separated practitioners, providing references such as guidelines for care and monitoring patient outcomes, adverse events, and practice patterns can help improve patient safety. Information technology can reduce error and the negative impact of error by the provision of critical information at the point-of-care, improved speed of response once an error has occurred and tracking the occurrence of errors to allow monitoring for trends and allow feedback to providers.[178] Importantly, though technology in the form of electronic health record best practice notices and other warnings can help alert clinicians to safety issues, alarm fatigue can also jeopardize patient safety.[179]

Smartphones have become one of the most rapidly adopted technologies with onboard technologies, such as Wi-Fi, Bluetooth, lights, microphones, cameras, accelerometers, and even barometers. Patient-facing apps may help engage patients with chronic pain in between (or perhaps instead of) traditional outpatient visits and empower them to take a more active role in the management of their ailment, to improve pain relief, to facilitate functioning, and to return to daily living.[180] Telemedicine, smartphone, or tablet that allows Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant text messaging or camera images may serve as a means to monitor patient wound status and be of value to a pain practice in which patients with invasive catheters are cared for at home.

It appears increasingly desirable to have a nationwide, internet-based monitoring program, such as the prescription drug monitoring program (PDMP), to avoid multiple prescriptions for opioids, improve patient safety, and distribute important information about patients' health.[181] Another example of the promise of safety improvement through innovative technology is in patient identification. Correct patient identification and elimination of wrong-site surgery have been identified by the WHO and TJC as a significant opportunity for improved safety.[182] The use of a bar coding system can virtually eliminate the potential for patient misidentification and can also diminish medication errors.

Imaging Technologies

Bedside administrative technologies are increasing in the field of healthcare. Imaging modalities in interventional pain medicine help accurately identify relevant structures, which intuitively appears to ensure safer interventional therapy in pain medicine. Ultrasound techniques, fluoroscopy, and computed tomography imaging are being used. There are indirect ways like nerve stimulation that help identify nerves and increase the likelihood of a successful neural blockade. However, they have limited sensitivity.[183] There are also direct methods to differentiate the properties of the target and those of the surrounding tissues. The safe use of ultrasound techniques has increased in the past years for performing nerve blocks. However, its impact on patient safety has been less clear.[184] Fluoroscopic guidance, with or without radiographic contrast, helps to assure extravascular catheter location or to detect intravascular needle perforation, and it can be used to prevent unintentional intravascular or subarachnoid injection of local anesthetics or steroids.[185] Techniques, like the use of an "optical" spinal needle that provides spectrophotometric information from the tip of the needle, can safely identify the epidural space and may be complementary to fluoroscopic imaging of the epidural space.[186] Brynolf et al. have shown that the detection of nerves with this optical reflectance spectroscopy is complementary to ultrasound and might replace nerve stimulation. It might also lower vascular complications while detecting intra-arterial needle tip placement.[187] Although image guidance has become a routine in pain medicine, there still insufficient evidence to prove that it increases the safety of the procedures.

Next Steps for the Pain Practitioner

Practitioners should work to discern practical ways to improve patient safety and the most efficient and economic means of practicing in congruence with the regulations and legislation now growing out of the public safety campaign. Whatever safety

improvement programs are chosen, they should be repeatedly evaluated for efficacy and abandoned if they are not efficient and effective. "Mistake-proofing" care will require minimizing variation in its delivery, monitoring every patient's course of care for error and adverse outcomes, and making care delivery systems within the clinic or practice setting as simple as possible to avoid the complexities that lead to variation and error.

Organizations that are considered "highly reliable" utilize five principles to achieve and maintain exemplary levels of safety that can be used by individuals:[188]

1. Preoccupation with failure, never being satisfied that they have not had an accident for many months or years
2. Resisting the temptation to simplify their observations and their experience of their environment
3. Sensitivity to operation, recognizing that the earliest indicators of threats to organizational performance appear in small changes
4. Commitment to resilience, recognizing that despite all best efforts and past safety successes, errors will occur, and safety will be threatened
5. Deference to expertise; when confronted by a new threat having mechanisms in place to identify individuals with the greatest expertise relevant to the situation

Box 6.4 lists specific targets that the pain practitioner can focus on to improve patient safety. It is critical to document these efforts and their results to ensure that resources are not wasted and portray the diligence of the practice when payers and regulators inquire about safety efforts.

• BOX 6.4 Interventions That May Improve Patient Safety in the Pain Clinic

Facility Procedures and Structure

- Routinely and repetitively conduct drills for emergency situations by assigning specific roles to personnel in the case of patient medical emergencies, facility emergencies (e.g. power outage, fire, earthquake, severe weather), and selected adverse events in patient care.
- If relocating or creating a new facility, locate it as near a hospital as possible. Arrange to create a legal transfer agreement with that hospital.
- Furnish the facility with in-wall piped oxygen and suction, and adequate lighting and space to allow full access to patients by sufficient personnel in the case of an emergency.
- Consider accreditation by the AAAHC, TJC, CARF, or another agency. If accreditation is not possible, consider an annual inspection by one of these agencies for evaluation of your facility and practice regarding safety.
- Daily cleaning should include bactericidal cleansing of all surfaces contacted by staff, patients, or family members of patients in all parts of the facility.
- Place hand cleanser dispensers in multiple locations readily available to all clinical and nonclinical staff.
- Drawers and supply cabinets should be clearly organized and standardized in their organization between rooms.

Medication Management

- Utilize available prescription drug monitoring programs (PDMP) to monitor and the frequency of renewals for opioids and sedatives.
- Monitor and document patient response to medication treatment.
- Use and adhere to written treatment agreements with patients for opioids and controlled substances.
- All medications used at the facility should be labeled (including an outdate once opened) and carefully read aloud before being drawn up and before administration.
- All syringes should be labeled in a standard manner regarding label color, font, size, and information on outdate.
- The facility should be regularly inventoried (weekly or monthly) for outdated medications and other supplies.
- Use medication reconciliation techniques to confirm doses and the frequency of all medications when there is a transition in caregiver, location, or date.
- Use computer technology to monitor for potential adverse drug events.
- Contract with a clinical pharmacist for consultation services as needed.
- Use protocols for monitoring the prescription of any medication that may lead to significant morbidity with continued use, such as non-steroidal anti-inflammatory drugs, opioids, tricyclic anti-depressants, and so on. These protocols should include timely and repetitive monitoring for known risks via either laboratory or electrocardiographic studies or mandated office visits.
- Communicate prescriptions of all medications to all practitioners providing care to your patient.
- Any adverse drug events should be reported immediately and recorded in a database that is regularly reviewed for trend analysis. The patient should be notified about the adverse event. The patient's other caregivers outside the practice should be notified about the adverse drug event.
- Prompt attention by staff should be focused on open discussion and adjustment of protocols and policies by the end of the day to avoid any repetition of errors that occurred either with or without an adverse drug event.

Technology

- Track the outcomes of all care. Use relational database technology to allow evaluation of outcomes for trends, both positive and negative. Do not make this a punitive system but provide information on outcomes to staff regularly to invite input on changes in the system that may avert negative events.
- Consider the use of an electronic medical record.
- Use technology to allow the integration of clinical and laboratory systems to ensure that all critical information is available at the point-of-care.
- Use a CPOE system that includes the transmittal of outpatient prescriptions directly to a pharmacy.
- Use a computer system to track patients' medications that has automated alerts regarding potential drug interactions and anticoagulant use.
- Use technology to provide practitioners with all necessary reference material for decision support (e.g. medication dose, cross-reaction, and toxicity information).
- Use technology to ensure accurate matching of patient identity, medication history, and current medications at each point-of-care. Consider the use of a bar code system.
- Create or obtain audiovisual (e.g. DVD) material about procedures and medications to allow patients to review them before obtaining informed consent for procedures or before beginning a new medication.

• BOX 6.4 Interventions That May Improve Patient Safety in the Pain Clinic (Continued)

Staff

- Establish a pattern of regular use of hand cleansing by all personnel.
- Create and enforce protocols for handoff of patients between practitioners.
- Create and enforce protocols for two-person patient identification interaction.
- Use standard teams with assigned roles for medical and invasive procedures.
- Involve all staff in discussions of quality and safety issues and invite open and non-punitive reviews of adverse events and trends with the freedom of each staff member to contribute ideas for the improvement of the system.
- Create a plan in advance to respond to adverse events, including honest discussions with patients and family and support for the staff involved.
- Do not allow employees to work beyond the limits of their education and training.
- Monitor, track, and report all practitioner work hours and do not allow them to extend beyond 80 h per week or for more than 16 consecutive hours.
- Maintain sufficient staffing to ensure adequate care for sedated or recovering patients. These staff levels should be equivalent to or more intensive than the local standard of care as used in hospitals in the area.

Procedures

- Use full barrier protection during invasive procedures.
- Administer appropriate prophylactic antibiotics.
- Use imaging technology when appropriate during invasive procedures.
- Use the minimum necessary contrast material.
- Develop and enforce the use of standard protocols for medical and invasive procedures, including sterile preparation and critical medication checks, such as anticoagulants.
- Use guidelines, checklists, or both.
- Develop and enforce protocols to ensure that invasive procedures are carried out at the correct site, including marking the patient's body area before preparation and a pause for verbal confirmation among all staff present of patient identification and procedural intent.
- Follow state and other applicable regulations regarding radiation safety.
- Avoid patient sedation beyond the loss of the ability to discern and communicate paresthesia or other changes in sensation during neuraxial or perineural procedures.
- Refer procedures that you rarely or never perform to higher-volume practitioners or facilities. Monitor the outcomes of these patients.
- Provide both written and audiovisual informed consent material and give patients time to review them and ask questions before obtaining informed consent for procedures.
- Use supplemental oxygen and monitor oximetry whenever sedation is used.
- Use supplemental oxygen and monitor oximetry whenever the prone position is used.
- Mandate and enforce that all patients have a driver before beginning either sedation or any procedure.
- Obtain written agreement from patients that they will not drive for 8 h following a neuraxial procedure, sedation, or any procedure that could impair their motor skills.

Extra Facility Considerations

- Maintain close interaction with any provider also involved in your patient's care.
- Provide information about prescriptions of all controlled substances that you have begun and any other medication or treatment interventions that you have made.
- Make direct phone contact with written confirmation regarding significant changes in condition or the treatment plan.
- Create a transfer agreement with a hospital to prepare for a patient emergency.
- Participate in the exchange of regular peer review of procedures and standards with other practitioners who have no economic stake in your practice or facility.

AAAHC, Accreditation Association for Ambulatory Healthcare; *CARF*, Commission on Accreditation of Rehabilitation Facilities; *NSAID*, non-steroidal anti-inflammatory drug; *TJC*, The Joint Commission.

Treatment Outcome Databases: Recording Adverse Events

Practitioners can help ensure their patients' safety by recording their outcomes and all adverse events in a database. There are many ways to measure outcomes, which are important to adequately reflect the provided quality. SF-36 or more comprehensive S-TOPS (Treatment outcome in pain survey) is used, among others.[189,190] Such an outcomes database or registry is vital for practitioners to discover their own best practices and to monitor for any trends that would reveal a lack of efficacy of therapeutic interventions. Simple recording of adverse events without affixing blame can provide opportunities for solo physicians and large groups to spot trends in which certain care patterns are associated with significant rates of error or even injury. Box 6.5 lists some of the adverse events that might be monitored in a pain medicine practice.

Some Practical Tips to Improve Patient Safety

In the environment of national safety initiatives that emphasize significant investment in information technology, some of the simpler steps in improving patient safety may be overlooked. For an office that engages in interventional therapy, there are parallels to the safety features needed in offices that perform any kind of surgery. Bridenbaugh[191] offered recommendations regarding safer office care, which include improved office emergency equipment, routinely updated and maintained by biotechnical personnel; training and certification of personnel in the delivery of medication and resuscitative techniques; use of written practice policies and procedures that are routinely reviewed with the staff, including emergency procedures; use of monitoring that conforms to the same levels as would be expected in an accredited ambulatory surgical center or hospital; guidelines for sedation and anesthesia

• BOX 6.5 A List of Potential Adverse Events to Be Monitored in a Pain Practice Safety Program

Procedural Events

Procedure on the wrong body part or location
Procedure performed on the wrong patient
Wrong procedure performed
Unintended retention of a foreign object in a patient
Product or device events
    Contamination
    Function other than intended
Intravascular air embolism
Infection following a procedure
Unexpected death following a procedure
Unexpected hospitalization within 24 h of a procedure
Unintentionally compromised nerve function following any procedure
Lack of consent or incongruous consent
Allergic reaction
Anaphylaxis
Abortion of a procedure-anxiety
Abortion of a procedure-other
Burn
CV-angina
CV-arrest
CV-congestive heart failure
CV-dysrhythmia
CV-electrocardiographic changes
CV-hypertension
CV-hypotension
CV-infarction
Death
Dehiscence of wound
Dizziness
Electrolyte abnormality
Failure to follow up or communicate laboratory, pathology, or radiology test results
Fainting
Fall
Fever-not malignant hyperthermia
Headache
Hemorrhage
Increased pain
Itching
IV site pain
IV site infection
Malignant hyperthermia
Neurologic change
No home care
No instructions given
No ride available
Physician delay
Patient delay
Respiratory arrest/apnea
Respiratory asthma
Respiratory pneumothorax
Respiratory pulmonary edema
Return to the operating room
Sepsis
Signed out against medical advice
Somnolence
Transient neurologic syndrome
Urinary retention
Viscus perforation

Non-procedural Care-Related Adverse Events

Serious adverse event secondary to a medication prescription
Any medication prescription error requiring follow up by a pharmacist or physician
Serious injury to a patient or other person secondary to misuse of a device or medication
Nerve injury, fall, or skin breakdown in an anesthetized body part following treatment
Hypoglycemia
Allergic reaction to medication or other treatment
Patient fall while on site at the facility for treatment
Patient fall while taking medication that may impair balance or mentation
Patient involvement in a motor vehicle accident subsequent or consequent to treatment
Any staff or patient injury while on site at the facility for treatment
Patient misidentification
Release of any patient to an inappropriate or incorrect caregiver
HIPAA privacy or security rule violation
Incomplete medication list documentation
Incomplete allergy list documentation
Incomplete problem list documentation
Incomplete or incorrect "other provider" list
Inability to access health records at the point-of-care

CV, Cardiovascular; *HIPAA*, Health Insurance Portability and Accountability Act; *IV*, intravenous.

that conform to those of the ASA; and compliance with any local or state standards of office safety and quality standards.

Accreditation

It is strongly recommended that every practitioner invite an independent agency to inspect their practice annually to provide advice about improving the quality and safety of care delivered there, even if formal accreditation does not ensue. Options include state health departments, and either TJC,[192] or the AAAHC.[193] Both of the latter will certify multiple- and single-specialty ambulatory surgical centers and physician practices and offices that practice pain medicine. If the program in question is a multi-disciplinary program, another accrediting organization to consider is the CARF,[194] which is willing to accredit what it terms "interdisciplinary pain rehabilitation programs."

Indeed, full accreditation or even just a letter from an inspector describing a practice's positives and negative attributes-assuming the former outweigh the latter-can be valuable in contracting with third party payers as a means of proving a salutatory commitment to patient safety and practice quality. Such accreditation has been used successfully to decrease liability insurance for a facility and malpractice insurance for both a facility and the physicians who are part of its practice or ownership group. Such documentation would be of value in the event of any later tort action concerning a patient's safety.

Avoidance of Provider Fatigue

Operator fatigue has been recognized as a potential source of error in many industries; the United States Congress and the IOM asked for work hour limitations to improve patient safety. Practitioners who have completed their training tend to work longer hours with less rest than is considered appropriate in almost any other work setting. This should be particularly concerning for those pain practices that employ interventional therapies. All

aspects of cognition are adversely affected by fatigue, although there is insufficient evidence to pinpoint a specific amount of rest as "enough" in medicine. Each practitioner is encouraged to create and follow personal and practice wide policies regarding continuous time spent in clinical activity.

Caution Patients Regarding Potential Impaired Ability to Drive

A controversial topic is the role a prescriber plays in the determination of the ability of his or her patients to drive an automobile. Most state regulations require healthcare practitioners to report any patients who have a medical or surgical impairment that would make them unsafe if they have not voluntarily given up driving.[195] This is a significant concern for practitioners whose practice has a large percentage of older patients, many of whom may have vision, hearing, or developing cognitive impairments that warrant concern about safety while driving a car.

Additional concerns for the pain practitioner are those patients who are using opioid medication, other psychoactive medications, or who undergo procedures that may impair their motor skills or mentation.[196,197] The real risk of driving in the setting of long term use of opioids is unclear, but there is likely impairment present for some patients.[198,199] Evidence exists that a subset of chronic noncancer pain patients has worse highway driving performance than matched health controls despite rating their subjective driving quality to be normal.[200]

Patients Undergoing Injection Therapy: Should They Have a Driver?

There have been no controlled studies of adverse consequences of driving post pain procedures, but there are several theoretical risks of driving, such as sensorimotor impairment after epidural steroid injection.[201] Many practitioners require all patients undergoing interventional therapy to have a driver for the following reasons:

1. Often, the patient's original diagnosis entails some degree of neural dysfunction. Therefore driving capability is probably already impaired.
2. Pain, which may increase during the initial treatment period, can cause mental distraction and muscle spasms that could impair driver focus and function.
3. The activity of driving very frequently will serve to exacerbate muscle spasm and is often among the activities that patients complain worsen their pain so that driving is on the list of activities that we ask our patients not to practice any more than is absolutely necessary during the days that treatment is in progress.
4. Theoretically, even those procedures that do not intentionally block neural transmission (e.g. an epidural steroid injection with only steroid and normal saline) may cause a diminished motor response because of either volumetric compression on nerve tissue or increased pain after the injection.
5. Patients are often asked to engage in therapeutic activities the day of their procedure, including the use of massage, bath, and relaxation therapy. The efficacy of these measures is opposed by the stress associated with the activity of driving.
6. Patients required to organize a driver for their return home may be less likely to immediately return to work after the procedure or ignore post procedure instructions.
7. Finally, with no definitive study in the literature showing that driving post injection therapy is safe and with plausible theoretic reasons to consider that such patients might be more prone to accidents, it is a reasonable and prudent precaution.

Opioid Stewardship

From 1999-2017, nearly 400,000 people in the United States died from an overdose involving an opioid, including prescription and illicit opioids,[202] becoming one of the most urgent public health threats of the country. Many factors across the healthcare system contributed to the problem, including the desire of clinicians and accrediting bodies to effectively manage patients' pain, third party payment issues, and a lack of knowledge of and/or access to a broader array of pain management options.[203] Although appropriate indications exist for prescribing opioids, including acute pain, active cancer treatment, palliative care, and end-of-life care, there is little evidence for long term use of opioids for the treatment of chronic, non-cancer pain.

Opioid Stewardship may be described as coordinated interventions designed to improve, monitor, and evaluate the use of opioids to support and protect human health.[91] Regardless of the setting or indication for opioid prescribing, individuals directly responsible for the treatment of pain and healthcare organizations should coordinate commitment and actions with the community to protect patients and the public through opioid stewardship efforts. A comprehensive system-level strategy that extends beyond education efforts toward opioid stewardship is warranted.[204–206] In 2018, the NQF developed a national opioid stewardship "playbook" outlining seven fundamental actions to support opioid stewardship in healthcare organizations:

1. Promote leadership commitment and culture.
2. Implement organizational policies.
3. Advance clinical knowledge, expertise, and practice.
4. Enhance patient and family caregiver education and engagement.
5. Track, monitor, and report performance data.
6. Establish accountability.
7. Support community collaboration.

The NQF Playbook is unfortunately available for purchase only but provides concrete and practical implementation examples, potential barriers, and suggested solutions and sample tools and resources from basic to advanced approaches that can be adapted to individual, organizational contexts. The Centers of Disease Control (CDC) and others have also issued guidelines for chronic opioid prescribing and data tracking tools to bring awareness, resources, and expertise to opioid stewardship efforts.[207,208]

An acute injury or a procedure is a common source of a patient receiving his or her first opioid prescription that may lead to long term use. The concept of a comprehensive opioid stewardship program at the systems level is growing and supported by TJC.[209] In 2019, a multi-professional group used literature review and consensus to develop a set of 19 valid and feasible quality indicators for opioid stewardship interventions in the hospital and emergency department settings.[210] Among the top priorities were naloxone administration, average dose of morphine milligram equivalents per day, use of long acting or extended release opioid in opioid-naïve patients, and length of prescriptions.

What to do When an Adverse Event Does Occur

This section intends to promote the use of methods to diminish the likelihood of error and avoid adverse events. Nonetheless, adverse events will happen. How should the practitioner respond? The initial impulse will most often be to deny the event, to "cover up" any role that error played in the outcome and at, all costs, not implicate any practitioner as culpable when communicating with

the affected patient. However, it is widely recommended that disclosure of medical errors be done as quickly as is reasonable with a sincere apology and a statement regarding how the healthcare team will avoid similar incidents in the future, even if not all of the details of the event are available at that time.[211]

The APSF emphasizes the importance of open and frank communication with the patient and family involved, with open answers to even difficult questions.[212] An attitude of learning and correcting error rather than blaming the practitioners involved, combined with complete honesty about the events that occurred, is suggested. Above all, a strategy for dealing with patient injury should be worked out in advance among all the practice participants. The APSF has placed an "adverse event protocol" on its website at www.apsf.org that is oriented toward an anesthetic adverse event (see drop-down list under "resource center" and click on "clinical safety tools"). It would provide guidance in the pain clinic and a clear statement that an error has occurred, details regarding that error, and how it will affect the patient's health.

The practice's adverse event plan should also include discussions with malpractice carriers and practice attorneys in advance of any events. Having a plan and confidence in it is the best approach to the management of any breaches of patient safety. Invariably, such events should be examined closely to find the system flaws that led to errors and improvement opportunities.

Conclusions

"Mistakes are a fact of life. It's the response to the error that counts. The only real mistake is the one from which we learn nothing."

~John Powell

Among these larger forces of business, government, and society, a lesson sometimes lost is that the individual practitioner *can* improve healthcare quality and safety. If practitioners identify those outcomes that are desired, employ the tenets of evidence-based medicine to find "best practices," and measure both their delivery of those therapies (process) and the results of those therapies (outcomes), then it is more likely that quality will improve.[213] Adherence to evidence-based "best practice" begins with the individual practitioner and is associated with significant improvement in patient outcomes, including mortality.[214]

QI initiatives can be fragmented, short-term, and challenging to sustain. In 2018, the WHO, The World Bank and the Organization for Economic Cooperation and Development, the National Academies of Science, Engineering and Medicine in the United States, and the Lancet Global Health Commission issued publications emphasizing the need to implement an infrastructure for learning to understand root causes and continually improve the quality of healthcare.[215] Pain medicine practitioners should align individual efforts with defined safety and quality strategies and plans at the national, regional, facility, and community levels to close the fragmented approach and facilitate the update of the national policy and strategy. Use active learning to quickly harvest internal and external best practices and create multiple feedback loops to enable a rapid response to improve care processes. Institutionalizing a culture of quality and patient safety through active learning to scale up evidence-based interventions increases awareness and diligence, contributing to the development of standards and measures to monitor and improve quality with team-based strategies and coordinated partner efforts.

Safety in medicine is a very complex problem, and progress may remain uncertain. For long term improvement in patient safety, we need a benevolent culture of safety in which healthcare providers can get an adequate education, including education on all available sources and technologies, with an understanding that the costs must be monitored.

Key Points

- The quality movement in healthcare continues to evolve. It is being driven by alarm among the public, payers, regulators, and the business community spurred by widespread evidence of unnecessary variation and potential unsafe care.
- The various stakeholders in healthcare define quality in different ways, and practitioners must consider these alternative attitudes as they work to improve and prove the value of their practices.
- At each clinic, a "culture of safety" must be established by creating new systems that will decrease the impact of human error on patient outcomes.
- If quality and safety are to be improved, they must be measured. Monitor and respond to measures of structure, process, and clinical outcomes using active learning strategies.
- Use QI and implementation science theories and tactics to apply practical approaches to continuous improvement in quality and safety.

Suggested Readings

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7

Education, Training, and Certification in Pain Medicine

JAMES P. RATHMELL, ANNE MARIE McKENZIE-BROWN

The Evolution of Pain Medicine as a Subspecialty

As medical knowledge expands, there is a natural progression toward specialization. No physician can become an expert in every field, yet there is discomfort with this inevitable narrowing of focus. The urge to both specialize and remain unspecialized dates back to the earliest recorded history in medicine. The first specializations were between barber surgeons and internists; a rivalry of sorts remains to this day. Writing about Ambrose Paré, the 16th century physician who elevated the role of barber surgeons to that of other physicians, the present-day surgeon and historian Sherwin Nuland reflected on the ongoing distinction between internist and surgeon[1]:

> *Surgery is an exercise in the use of the intellect. Heckling internists, with tongues barely in check, would prefer that surgical specialists be viewed merely as dexterous craftsman who carry out the routing errands assigned to them by their more cerebrally endowed medical overseers. I attribute this teasing raillery to a kind of good-natured fraternal envy, not so much of our celebrity status, but rather of the visibility of the cures we surgeons achieve and the particular personal gratification we have while doing it.*

In the United States, anesthesiology has progressed toward further specialization, first with the establishment of critical care, then pain management (now pain medicine), and more recently pediatric anesthesiology, cardiothoracic anesthesiology, regional anesthesia, and acute pain medicine. With specialization comes a conscious effort to focus practice so that one becomes intricately familiar with a more limited realm. The obvious result is the loss of the skills and knowledge needed to practice in the broader parent specialty. In pain medicine, many now view this as a full-time vocation. The scientific meetings and journals that keep pain medicine specialists up to date have little overlap with those designed to serve anesthesiologists practicing in the operating room. A common thread between the technical skills needed in the pain clinic and those required for anesthesiology in the operating room is expertise in neural blockades. With the advent and portability of ultrasound guided blockade, procedures initially reserved for the perioperative setting, e.g. transversus abdominus plane (TAP) blocks, are now being adapted for use in the treatment of chronic pain conditions.[2] The pain medicine practitioner must acquire a vastly different skillset from those practicing anesthesiology, including expanding their skills as diagnosticians. Pain physicians need to be able to distinguish between conditions appropriately treated with injections and those requiring surgical intervention, e.g. lumbar radicular pain associated with rapidly progressive neurologic deficits. They need to know when to hold off on interventional therapies and pursue further diagnostic testing in patients who display "red flag" signs or symptoms consistent with malignancy, infection, and other serious disorders. The skills of a pain physician must also include expertise in having difficult conversations and the ability to coordinate and collaborate with other specialists.

Much has been written about the origins of pain medicine as a distinct discipline, and anesthesiologists have played a primary role since its inception.[3] It started with the introduction of effective general anesthetics in the mid-19th century, when surgical pain could be separated from surgery. Almost 100 years later, the late John Bonica, an anesthesiologist and recognized father of the specialty that we now call pain medicine, developed his career by promoting multi-disciplinary pain care and formal training of specialists. From his life's work, we now have extensive ongoing efforts to recognize and treat pain effectively, train subspecialists, and conduct basic and clinical research to understand pain and its treatment further. The International Association for the Study of Pain, founded in 1974, its United States chapter, the (now dissolved) American Pain Society, and the journal *Pain* are legacies left by Dr. Bonica for our patients.

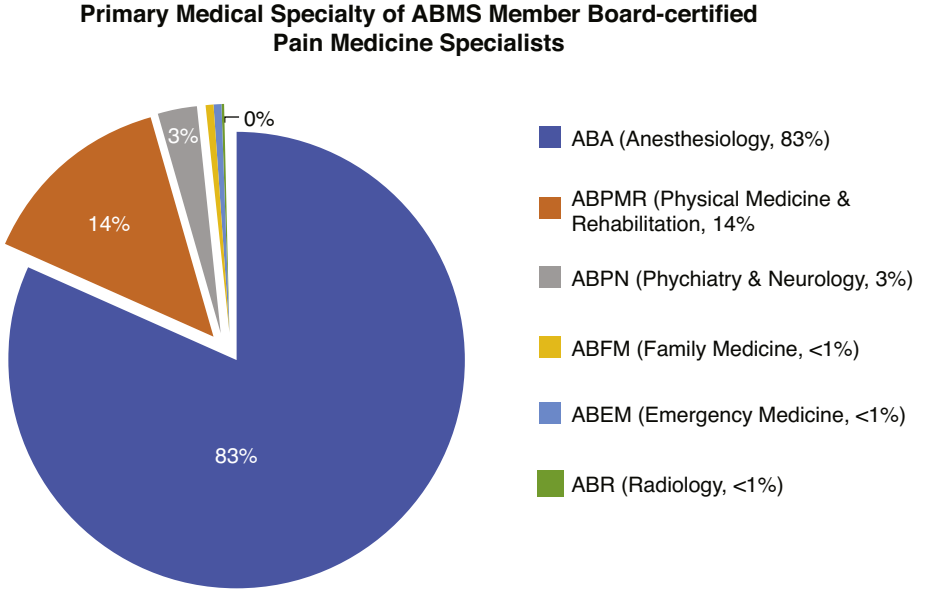
Accredited fellowship training in pain medicine is a relatively recent development. Before 1992, training was frequently obtained in academic anesthesiology departments, including those of Bonica, Bridenbaugh, Carron, Haugen, Moore, Raj, Winnie, and others, and subsequently in programs run by their trainees. These unaccredited programs advanced the specialty, widened interest in pain medicine as a career, and propagated pain care in smaller and smaller communities across the country. Outside the United States, this type of informal training remains the rule for those seeking expertise in pain medicine. In the United States, the American Board of Anesthesiology (ABA) developed an interest in certifying pain medicine specialists following their training. Through the leadership of Dr. William Owens in his roles in both the ABA and the Accreditation Council on Graduate Medical Education (ACGME) and through his representations of the subspecialty to the American Board of Medical Specialties, formal training programs were accredited, and physicians were certified. Drs. Stephen Abram and John Rowlingson were both key members of the group that assisted Dr. Owens in moving the new subspecialty forward.

The first programs were accredited by the ACGME in 1992. The number of ACGME-accredited programs and trainees in accredited programs has grown steadily over the past decade, and there are now more than 100 training programs that turn out about 300 new pain specialists each year. Working in parallel with ACGME, the ABA developed a subspecialty certification examination in pain medicine, first named the "Certificate of Added Qualifications in Pain Management" and now titled "Subspecialty Certification in Pain Medicine." The first examination was given in 1993. This examination is written and edited by a multi-disciplinary group of experts in the fields of anesthesiology, physical medicine and rehabilitation, neurology, and psychiatry. The number of candidates taking the examination has grown steadily since the initial examination (see Fig. 7.1). The fastest growing cohort of examination candidates have been from the specialty of physical medicine and rehabilitation (see Fig. 7.2).

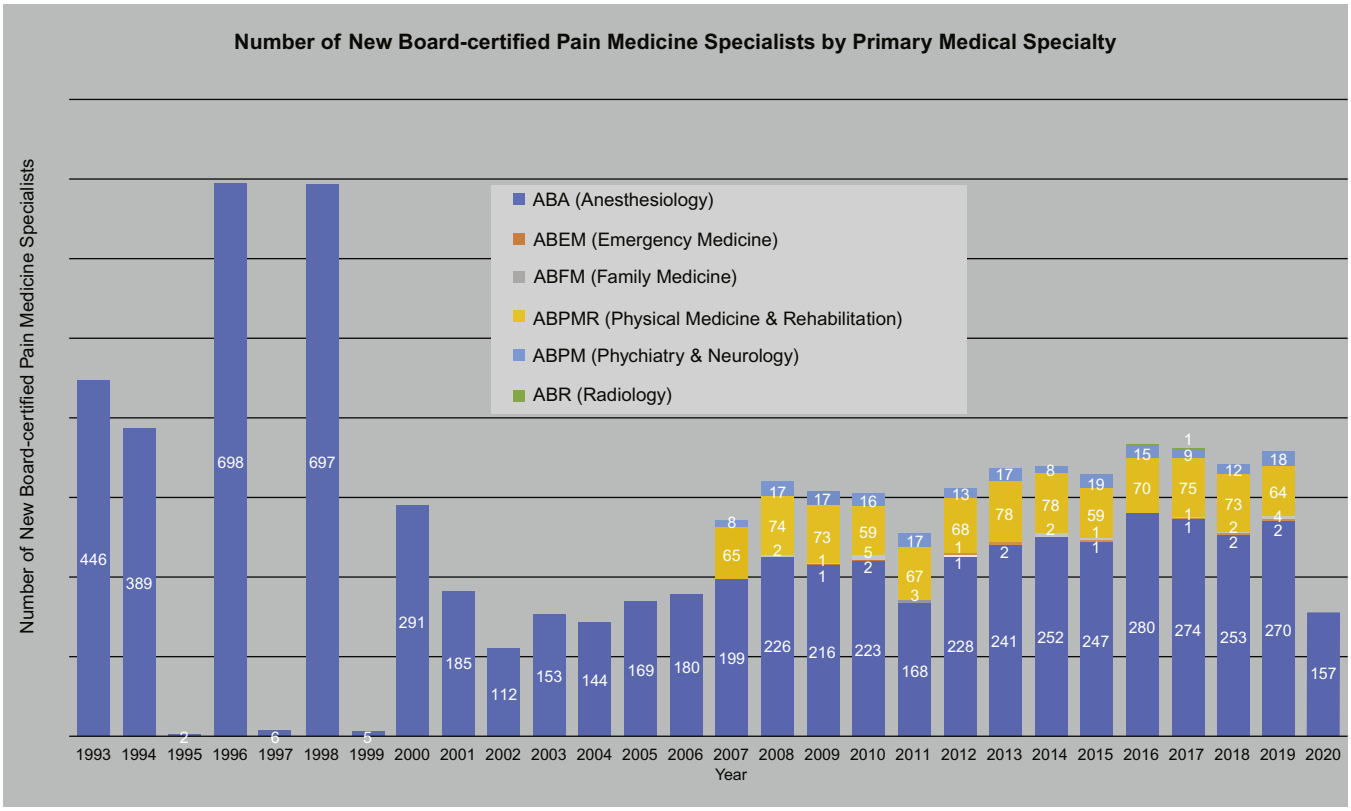
Dr. Bonica's original push to develop multi-disciplinary pain care recently evolved into a collaboration between four specialties that agreed to a single and unified set of program requirements for all ACGME-accredited pain fellowships, regardless of the sponsoring specialty. The ACGME Residency Review Committees for Anesthesiology, Neurology, Physical Medicine, and Rehabilitation and Psychiatry agreed on these requirements in late 2005, and the ACGME board approved their implementation for 2007.[4] These requirements have standardized pain fellowship training programs. After the introduction of new training requirements in 2007, several programs closed because of unwillingness to adopt a multi-disciplinary approach, and thus only the more comprehensive programs were left to continue the training of physician pain specialists (see Fig. 7.3). Programs have begun to produce more comprehensive and multi-disciplinary focused physicians from a broader range of primary disciplines. Other groups also encourage a more comprehensive approach to pain care, with the linked American Academy of Pain Medicine and the American Board of Pain Medicine likewise devoting energy to a multi-disciplinary approach. Equally important in the evolution of the discipline is the creation of academic physicians within the fellowships who undertake research programs to add new knowledge to guide clinical practice in this area of medicine.

Pain and its consequences draw on resources from all medical disciplines. Dr. Bonica's experiences during World War II suggested that each medical specialist had unique expertise to bring to patients suffering pain, hence his consistent and effective promotion of a multi-disciplinary process for pain care. Thanks largely to Dr. Bonica, anesthesiology has led the development of formal training programs. Indeed, most currently accredited programs reside within academic anesthesiology departments, and most program directors are anesthesiologists. Specialists from other disciplines have also focused their clinical and research efforts on pain. The most obvious example is neurology, from which the majority of clinical treatment and research on headache has arisen. The field of physical medicine and rehabilitation has also had a focus and expertise on functional restoration, and physiatrists lead many chronic pain rehabilitation programs. The pain expertise of these specialties brings together complementary concepts for overlapping areas in expertise, e.g. in the treatment of low back pain and chronic headache, the most common causes of chronic pain in the United States and internationally.[5] Moreover, psychiatrists and psychologists have been closely involved when pain, depression, and substance abuse overlap. During the last decade, specialists from these other disciplines have been seeking subspecialty training in pain medicine with increasing regularity. Close interaction with fellows from specialties outside their own has led some fellowship graduates to join or start multi-disciplinary pain practices upon graduation, continuing the collaborative care they learned in their training. Pain societies, such as the American Society of Regional Anesthesia and Pain Medicine and the American Society of Interventional Pain Physicians, once anesthesiology based, are now multi-disciplinary.

The range of practitioners declaring themselves pain medicine specialists is extraordinary, from clinics that provide largely or solely cognitive-behavioral approaches to chronic pain through functional restoration programs all the way to the type of clinic that offers nothing more than injections of various sorts. "Interventional pain medicine" is a phrase that has been coined for techniques that involve minimally invasive treatments and minor surgery as part of their application, including neural blockade and implantable analgesic devices. Despite the paucity of scientific evidence to guide pain practitioners, particularly evidence to support the use of many interventional modalities, many techniques with efficacy based on limited observational data have been adopted into widespread use. Many organizations have published guidelines on the appropriate use of interventions and other therapies to treat pain conditions.



• **Figure 7.1** Primary specialty of board certification of diplomates receiving subspecialty certification in Pain Medicine through a member board of the American Board of Medical Specialties (ABMS). ABA, American Board of Anesthesiology; ABEM, American Board of Emergency Medicine; ABFM, American Board of Family Medicine; ABPMR, American Board of Physical Medicine and Rehabilitation; ABPN, American Board of Psychiatry and Neurology; ABR, American Board of Radiology (Data courtesy of the American Board of Anesthesiology, July 2021).



• **Figure 7.2** Trends in the number of new subspecialty board-certified diplomates in pain medicine recognized by the American Board of Medical Specialties (ABMS) and their primary discipline of ABMS board certification. ABA, American Board of Anesthesiology; ABEM, American Board of Emergency Medicine; ABFM, American Board of Family Medicine; ABPMR, American Board of Physical Medicine and Rehabilitation; ABPN, American Board of Psychiatry and Neurology; ABR, American Board of Radiology (Data courtesy of the American Board of Anesthesiology, July 2021).

Still, there is no single practice pattern that pain specialists can point to as being the correct way to treat patients with chronic pain. Training programs vary widely in the scope of what they train practitioners to do. The best pain medicine practitioners strike a reasonable balance between interventional and non-interventional management. This practice pattern is sustainable, and those adopting a balanced style of practice will be able to adapt to the evolving scientific evidence that appears in support of pain treatment, regardless of the type of treatment. A balance between treatment modalities also allows practitioners to switch from one mode to another or to incorporate multiple treatment approaches simultaneously. The use of these interventional modalities is just one part of the expanding armamentarium of a skilled pain practitioner, which now also includes complementary and alternative therapies.

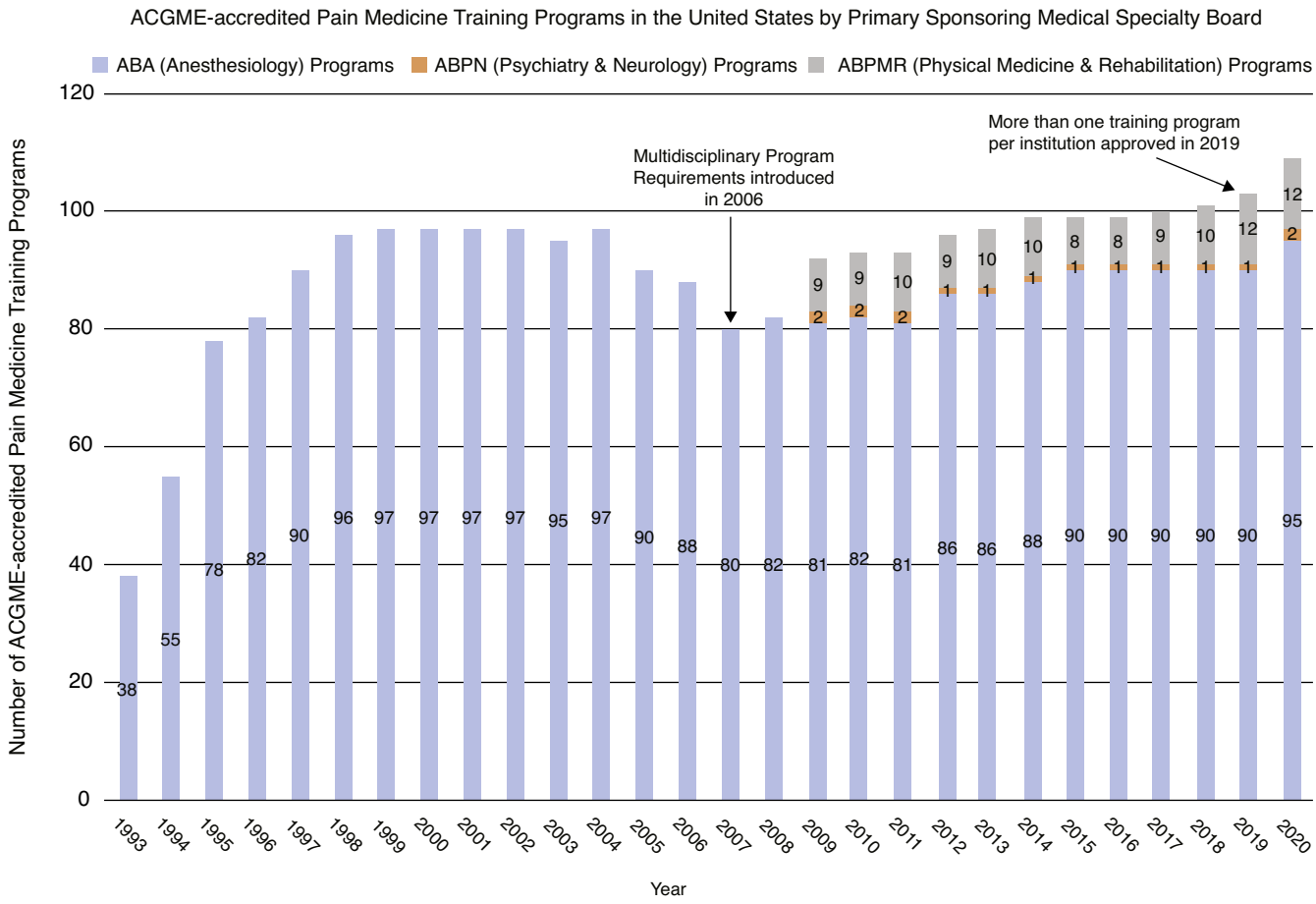
Training and Credentialing in Interventional Pain Medicine

In our rapidly changing world of modern health care, new technologies are appearing at a dizzying rate. Many of these new treatments require physicians to acquire detailed new knowledge and technical skills. The introduction of new techniques typically extends from centers in the public or private sector, where the ideas are conceived and tested in a limited realm among innovators. From there, anecdotes can often take over, and many techniques in pain medicine have blossomed into widespread use with nothing more than word of mouth to propagate their use. The use of pulsed radiofrequency and intradiscal electrothermoplasty[6] for the treatment of pain are examples where clinical application preceded detailed clinical testing.[7]

In the United States and Europe, industry often leads innovation by testing and initiating the introduction of new devices. When the innovation appears to have merit in limited trials, many devices are introduced to the market with approval through the Food and Drug Administration's 510K "substantially similar device" process with little or no data regarding efficacy. Once on the market, the means by which practitioners decide to adopt new technologies, the speed of progression of these new techniques, and—of great importance—the means by which practitioners gain enough expertise to introduce new techniques into their own practice are all highly variable and seemingly without any rational or consistent approach.

Interventional pain medicine is evolving as a distinct discipline that requires detailed new knowledge and expertise. Familiarity with radiographic anatomy for performing image-guided injections and the minor surgical skills needed to implant devices such as spinal cord stimulators and intrathecal drug delivery systems are just a few of the techniques that practitioners must master. As we set out to introduce new interventional techniques into our own pain practices, we must be sure that we have been properly trained to perform these techniques in a manner that ensures safety and success.

Adequate exposure to these newer treatment alternatives during the fellowship training period is necessary to ensure appropriate application and optimize patient outcomes. ACGME requires demonstration of competence for peripheral nerve blocks, neurolytic and neuraxial procedures, and neuromodulation. For techniques that are now widely accepted as a core element of pain practice, we must ensure that our trainees gain enough experience to conduct



• **Figure 7.3** Trends in the number of pain medicine fellowship training programs accredited by the Accreditation Council for Graduate Medical Education (ACGME) since the first program were established in 1992 (Data courtesy of the American Board of Anesthesiology, July 2021).

these procedures independently. One key element of the ACGME deliberations about unified pain training is to acknowledge that not all pain fellows will have experience in the wide variety of interventional techniques. Acquisition of competence in these procedures may be more easily acquired in those with a background in an interventional primary specialty. Instead, it is hoped that these fellows will gain an understanding of all available options for patients with pain and yet demonstrate and have competence documented in only techniques for which formal training is made available during fellowship training.

It is difficult to define the techniques that are core for a pain practitioner. However, it does seem that detailed knowledge of the radiographic anatomy of the spine and the minor surgical expertise required to implant spinal cord stimulators and permanent intrathecal drug delivery systems are among the skills that most practicing pain physicians would expect a new graduate from a pain fellowship program to have. New techniques are appearing at a staggering rate, and we cannot rely on pain fellowship programs to provide all the technical training needed. More robust standards for documentation of minimum training following fellowship programs are also urgently needed. Some pain practitioners believe that too many of their colleagues find it perfectly acceptable to attend a single brief weekend course and then introduce a highly technical new treatment into practice without additional study, training, or oversight.[8] Practitioners themselves must take the lead in obtaining adequate training *before* proceeding with any new and unfamiliar technique. A weekend workshop is just a start, often a good start, particularly in the years following fellowship training. The best workshops will give practitioners a detailed understanding of anatomy, pathophysiology of disease related to use of the new technique, patient selection, conduct of the procedure, outcomes, and avoidance, management, and recognition of complications. These workshops are increasingly accompanied by links to training videos that may be viewed and reviewed at a later date. In Spring 2020, during the COVID pandemic, the use of telehealth dramatically increased, and organizations offered a variety of educational webinars, often free of charge, discussing techniques and strategies for interventional procedures such as ultrasound-guided neural blockade and neuromodulation. Box 7.1 is a suggested method for practitioners to introduce a new technique into clinical practice.[9]

Future Directions

The field of evidence-based medicine has emerged as a new paradigm to guide practicing physicians. This field aims to educate practitioners on how to frame specific questions based on the clinical problems that they encounter every day. They then venture to the published scientific literature with focused questions on prevention, treatment, and diagnosis of a specific clinical condition. Many evidence-based medicine centers offer concise and periodically updated summaries on specific clinical conditions. The idea is to get the best information available to practicing clinicians.

• BOX 7.1 Suggested Training and Experience When Introducing a New Technique Into Clinical Practice

Study the new technique and the published literature and gain detailed knowledge of all aspects of the technique.

Attend a workshop, preferably a hands-on cadaver-based workshop that allows the introduction of the technique in as realistic a setting as can be assembled. Review the post workshop videos, if available.

Plan adequate time for your initial procedures.

Get help at the bedside during the initial performance of new procedures—perhaps another experienced practitioner at your institution or an invited expert to assist or team up with a colleague in a related discipline.

Inform your patients that you are introducing a new technique and include this discussion as part of the informed consent process.

Scrutinize your outcomes in the initial stages of using any new technique and compare them with those of your colleagues and the published literature.

Reprinted with permission from Lubenow TR, Rathmell JP. Let's take a rational approach to technical training in pain medicine. *Am Soc Anesth Newsl.* 2005;69:6-8.

They describe the best available evidence, and if there is no good evidence, they say so. In pain medicine, we are faced with an expanding array of treatment options that strike us as logical developments that s*hould* provide pain relief for our patients. However, there is a dearth of clinical evidence to guide rational choice and application of many emerging treatments. So how are we to decide when to apply them?

In 2003, Merrill[10] presented an analysis of the state of evidence guiding the use of interventional treatments in the field of pain medicine. He pointed out the frequent flaws in existing studies (largely the lack of valid comparators, such as no treatment) and concluded that "the practice of invasive pain medicine teeters at a particularly critical juncture…crippled by a lack of vigorous self-evaluation of its role in the treatment of chronic pain." Merrill explained the means by which we, as scientists and clinicians, can build a better body of evidence for the treatments we are using. A recent publication also addressed this lack of scientific rigor for interventional therapies. They commented that poor research results might in part reflect the inherent challenges in blinding and patients refusing the possibility of not receiving an intervention.[11] However, the field of pain medicine is relatively young, and although randomized clinical trials are still lacking for many treatments, some are starting to emerge. The Minimally Interventional trial failed to demonstrate long term efficacy for radiofrequency denervation compared to exercise for low back pain.[12] With the advent of paresthesia free spinal cord stimulation, randomized controlled trials showing promise for neuromodulation in certain pain populations are now in publication.[13,14]

New treatments evolve slowly. Application of the scientific method in clinical medicine begins with observation, perhaps a chance observation that a certain drug typically used for another purpose provides analgesia to a given patient. If the drug is readily available, a clinician may choose to treat other patients with similar conditions. If academically minded, the clinician may choose to report the limited success in a case series. Case series are a valuable beginning, the very beginning of emerging new ideas. If the problem is uniform and prevalent enough, the new treatment may gain the attention of investigators willing to assemble a randomized clinical trial. All too often, sound treatments are never tested because of a lack of interest or funding. Those that are tested tend to be under patent, and the manufacturer proceeds with large trials understandably in the hope of financial return in the event that the treatment proves useful. Patients who are suffering from severe and intractable pain are desperate and can easily be convinced that desperate measures, however new or unproven, are warranted.

How then are we to proceed? Our patients are begging for us to try anything that offers a glimmer of hope in reducing their pain, and we as scientists embrace the rigor of the scientific method and want desperately to do what is best for our patients. We have treatment after treatment that makes logical sense and shows early promise in case series and observational studies, but few data that support an evidence-based approach to practice. Using acute low back pain with sciatica as an example, several evidence-based reports have emerged to guide clinicians.[15] The only modalities that are rated as "beneficial" or "likely to be beneficial" are advice to stay active and the use of non-steroidal anti-inflammatory drugs, behavioral therapy, and multi-disciplinary treatment programs. Opioid analgesics, acupuncture, back schools, epidural steroid injections, and spinal manipulation were all judged to be of "unknown effectiveness." Nevertheless, in actual clinical practice in the United States, a short course of an opioid analgesic plus early intervention with epidural steroid injections is common. To complicate matters, the use of fluoroscopic guidance to direct injections to the affected level via an interlaminar or transforaminal approach has gained widespread acceptance, but with limited studies to guide us as clinicians. Those with persistent pain and contained disk herniations now have a dizzying array of treatment options, with only uncontrolled observational studies that suggest effectiveness.[16] The new devices are intellectually appealing and minimally invasive, yet only open surgical diskectomy has proved superior to conservative management in patients with persistent sciatica secondary to intervertebral disk prolapse.[17]

The evidence-based medicine movement gives little guidance to practitioners whose tools are still under development. They simply remind us that scant evidence regarding many of our techniques exists. Without declaring a moratorium on all interventional pain techniques, Merrill[9] offers the individual practitioner advice: monitor your own outcomes with valid measures, be more reflective and systematic in studying your own outcomes and patterns of care, and provide this information to your patients as part of the decision-making process. As pain practitioners, we have an expanding range of treatment options available to us, few with convincing evidence of efficacy superior to that of alternative treatments. We must evaluate each patient and use the limited evidence available to us today to guide compassionate and rational, if not evidence-based, use of therapy for our desperate patients.

The urgent need for expanded clinical research in pain medicine, coupled with recent efforts to improve multi-disciplinary training, is straining the ability of training programs to adequately provide the needed education and research experience for pain medicine fellows in the course of a one year fellowship. The ACGME and ABA are currently working to further restructure pain medicine training to accomplish these goals (for a review, see Rathmell[18]). The idea is to provide more comprehensive and multi-disciplinary training and require meaningful research experience during fellowship training. With this approach, we will create a more homogeneous group of pain medicine specialists who emerge with similar knowledge and skills, regardless of the parent discipline in which they trained. This will move us toward improving the consistency and quality of care of patients with acute, chronic, and cancer-related pain.

Key Points

- The first multi-disciplinary pain clinic was established by the late Dr. John Bonica. The International Association for the Study of Pain, founded in 1974, its United States chapter the (now dissolved) American Pain Society, and the journal *Pain* are his legacies.
- The initial accredited pain medicine fellowship programs were based on anesthesiology programs. The ACGME Residency Review Committees for Anesthesiology, Neurology, Physical Medicine, and Rehabilitation and Psychiatry agreed on standard multi-disciplinary requirements in late 2005, and the ACGME board approved their implementation for 2007. Several programs closed, and the more comprehensive programs continued the training of physician pain specialists. These programs have begun to produce more comprehensive and multi-disciplinary focused physicians from a wider range of primary disciplines.
- Detailed knowledge of the radiographic anatomy of the spine and the minor surgical expertise required to implant spinal cord stimulators and permanent spinal drug delivery systems are among the skills that a new graduate from a pain medicine fellowship program is expected to have.
- Together with the ACGME, the ABA developed a subspecialty certification examination in pain medicine, first named the "Certificate of Added Qualifications in Pain Management" and now titled "Subspecialty Certification in Pain Medicine." The first examination was given in 1993, and the number of candidates taking the examination has steadily grown.
- Many devices have been introduced to the market with approval through the Food and Drug Administration's 510K "substantially similar device" process with little or no data regarding efficacy. The means by which practitioners decide to adopt new technologies, the speed of progression of these new techniques, and the means by which practitioners gain enough expertise to introduce new techniques into their own practices are all highly variable. Rational steps in incorporating a new interventional technique into someone's practice are outlined in Box 7.1.
- Efforts to provide multi-disciplinary training and the need for clinical research are straining the ability of training programs to provide the education and research experience for pain medicine fellows in the course of a one year fellowship. The ACGME and ABA are currently working to further restructure pain medicine training to accomplish these goals.

Suggested Readings

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PART 2

Basic Considerations

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8

Neurophysiology of Pain: Peripheral, Spinal, Ascending, and Descending Pathways

KARIN N. WESTLUND

Introduction

The neural circuits that are responsible for pain and the reactions to pain[1] can be termed the *pain* system,[2–4] or perhaps more appropriately, the *pain systems*. The pain systems include (1) peripheral neurons with a set of peripheral receptive elements, the nociceptors, (2) numerous central neuronal relay pathways, and (3) sets of integrative neurons that impose excitatory or inhibitory influences on nociceptive information at numerous levels of the neuraxis.

While functioning under normal conditions provides warning information vital to tissue protection, and if pain persists, maladaptive neuroplastic reconfiguration occurs at the synapse and in specific brain regions creating a chronic pain state. When expansion to other systems such as affective, aversive, learning, and memory occurs, chronic pain, anxiety, and depression can result.

The initial reception of inputs perceived by the brain to be painful occurs at the peripheral terminations of sensory axons, the nociceptors that transduce noxious mechanical, thermal, and chemical stimuli into action potentials. Sensory nerve axons transmit information about internal or external stimuli that are noxious, distressing, or damaging to the second order neurons located at the corresponding spinal cord or brainstem level (i.e. lumbar spinal cord for leg input, thoracic spinal cord for stomach lining input, and trigeminal spinal nucleus for face input). The spinal excitatory (glutamatergic) and inhibitory ([γ]-aminobutyric acid-ergic [GABAergic] and/or glycinergic) interneurons provide a complex integrative network circuitry influencing the incoming nociceptive input received by nociceptive spinal dorsal horn projection neurons. As examples, the projection neurons and the inhibitory neurons have excitatory drive from spinal interneurons and/or from primary afferent nerve fibers. Spinal inhibitory interneurons may mediate pre-synaptic inhibition at the terminals of primary afferent nerve fibers as well as pre- and post-synaptic inhibition of spinal excitatory interneurons. Nociceptive spinal dorsal horn projection neurons are modulated further by long, descending facilitatory and inhibitory pathways.

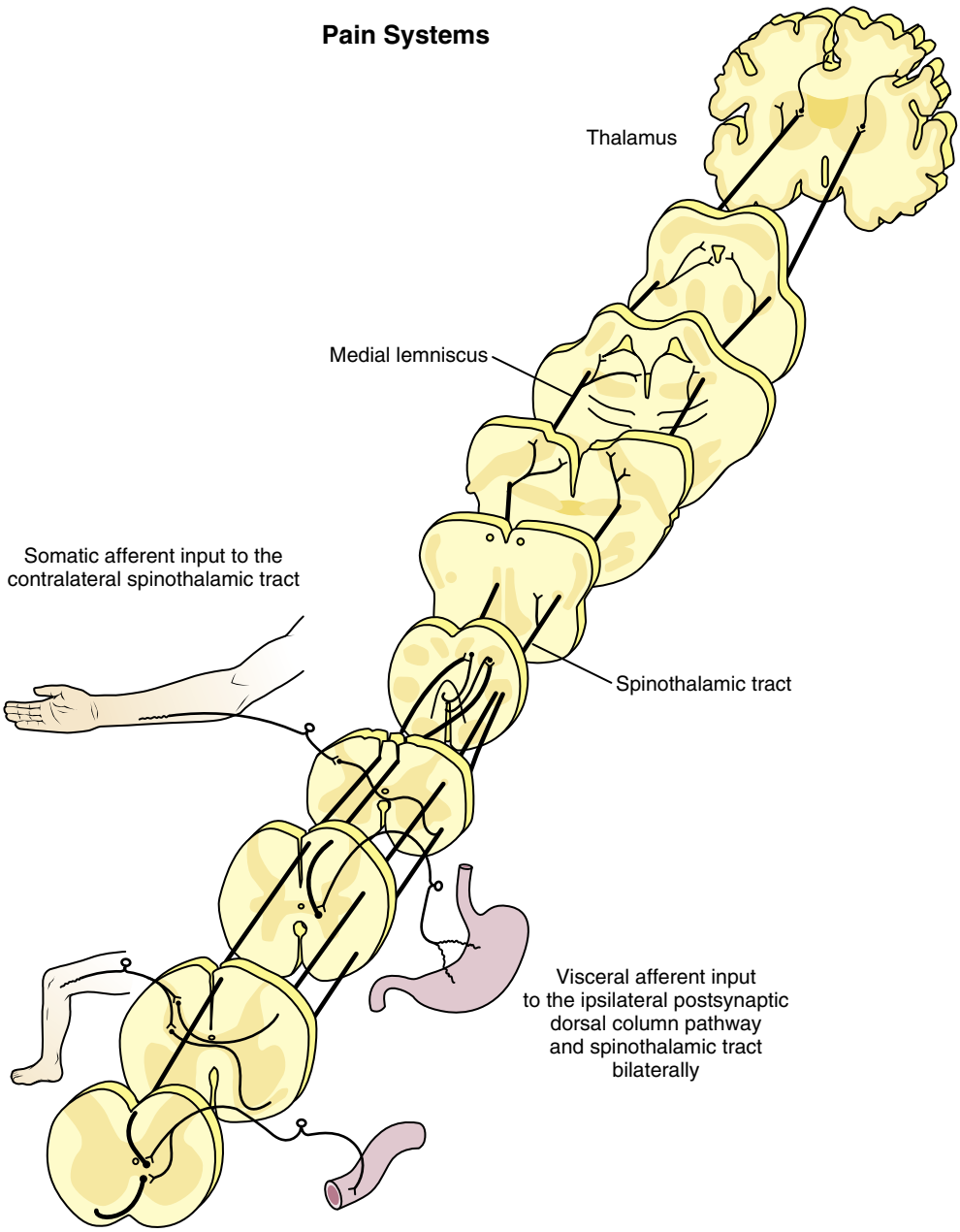
Nociceptive signals are then transmitted by the pain system projection neurons to other integration sites in the brainstem and higher brain via collateral input. The primary integration of site-specific sensory information in the brain occurs in the thalamus that then relays the information for cortical site perception. A variety of coordinated responses are generated in response to relay of nociceptive information to numerous other brain neuronal sites and circuitry activating integrative excitatory and inhibitory mechanisms. Beyond cortical awareness of pain, processing occurs to provide protective somatic and autonomic reflexes, endocrine actions, emotional responses, as well as learning and memory about the event.

In addition to pain and pain reactions, the brain centers that receive nociceptive information provide either negative or positive feedback that can reduce or accentuate pain and pain reactions. Negative feedback to the spinal cord circuitry is mediated by descending pathways that are often called the "endogenous analgesia system." The mechanism and pathways responsible for the accentuation of pain and pain reactions, referred to as *central sensitization,* can involve increased responsiveness at all levels of the pain systems, including the peripheral nociceptors, sensory neurons, the spinal cord, brainstem, and higher centers. The net effect of the positive and negative circuitry alterations leads to the perceptual experience of "pain," but over time the discomfort of continuing pathologic chronic pain can result in increased anxiety, depression, and disability.

Nociceptors

Peripheral Receptive Elements

The initial reception of noxious inputs perceived to be painful occurs at the specialized endings of primary afferent sensory neurons known as *nociceptors*. Reception of noxious input occurs at the functionally specialized free nerve endings of the skin, muscle,[5] joints,[6,7] viscera,[8,9] and dura (Fig. 8.1).[10] Nociceptive endings are also located in the fascia and adventitia of blood vessels.[11] Nociceptor subtypes respond best to mechanical (mechanical nociceptors); mechanical and thermal (mechano-thermal nociceptors); or mechanical, thermal, and chemical stimuli (polymodal nociceptors).[12,13] Common types of cutaneous nociceptors are Aδ mechanoreceptors and C polymodal nociceptors, which relay the transduced information about potentially harmful input via Aδ and C-fibers, respectively.[14,15] Glutamate receptors, as well as μ and δ-opiate, substance P (SP), somatostatin,



• **Figure 8.1** The pain systems convey input from somatic structures, as well as from viscera and other deep tissues, via peripheral nerves. Afferent nerve fibers carrying nociceptive information have free nerve endings in peripheral tissue and terminate in the superficial spinal cord dorsal horn. Information about pain is relayed through at least one synapse to cells in the spinal cord dorsal horn. Two parallel ascending pathways provide the information to integration centers in the thalamus, which provide the information to cortical regions. Input primarily from somatic structures is relayed to spinothalamic tract cells whose axons cross the midline and ascend in the lateral and ventrolateral spinal white matter as the spinothalamic tract. As the spinothalamic tract courses through the brainstem, collateral fibers innervate various brainstem centers involved in providing responses to nociceptive input on its path to the thalamus. Nociceptive input arising from visceral structures is relayed by post-synaptic dorsal column cells whose axons course in the dorsal columns. After a synaptic relay in the dorsal column nuclei and crossing to the opposite side of the brainstem, the medial lemniscus carries visceral nociceptive information to the thalamus. Both these routes are somatotopically arranged throughout their length.

and vanilloid receptors, have been identified immunohistochemically on the peripheral endings of cutaneous nerve fibers.[16–20] Neuroactivators released by tissue injury (ATP, bradykinin, nitric oxide, H+) and cytokines (tumor necrosis factor [TNF]α, interleukin [IL]-1β, IL-6) released by macrophages, neutrophils, and mast cells drawn to an injury site produce amplified peripheral nerve responses or peripheral sensitization (i.e. enhanced nociception).

Peripheral Nerves

The small axons that relay information about noxious input from the skin and other tissues to the central nervous system (CNS) fall characteristically into the range of unmyelinated fibers with conduction velocities less than 2.5 m/s in the case of C-fiber (or group IV) nociceptors (Fig. 8.2),[21] and small fibers wrapped in a

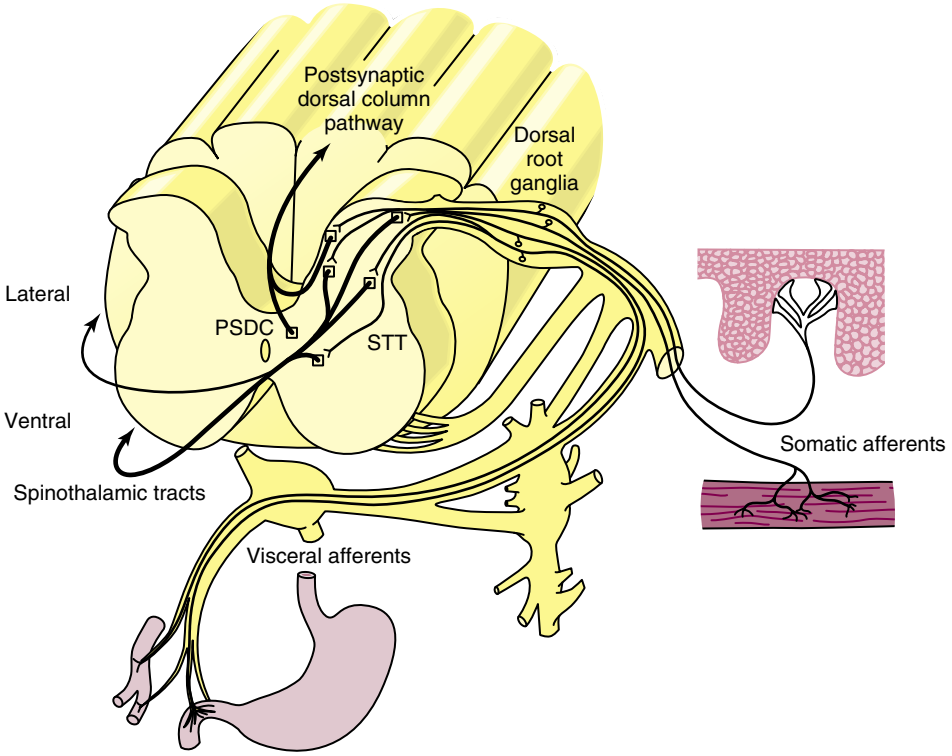
• **Figure 8.2** Peripheral nerves conveying information about pain are either small, slowly conducting fibers found unmyelinated in bundles or medium sized axons with thin myelin, which provides a higher conduction velocity.

thin layer of myelin produced by Schwann cells with a conduction velocity of 4–30 m/s in the case of the Aδ fibers (or group III).[22] Primary afferent C-fibers are more numerous than myelinated primary afferents in peripheral nerves. For example, in dorsal roots, the ratio of C-fibers to A fibers is about 2.5:1,[23] and in joint nerves (after sympathetic postganglionic axons are removed by sympathectomy), the ratio of C-fibers to A fibers is 2.3:1.[24]

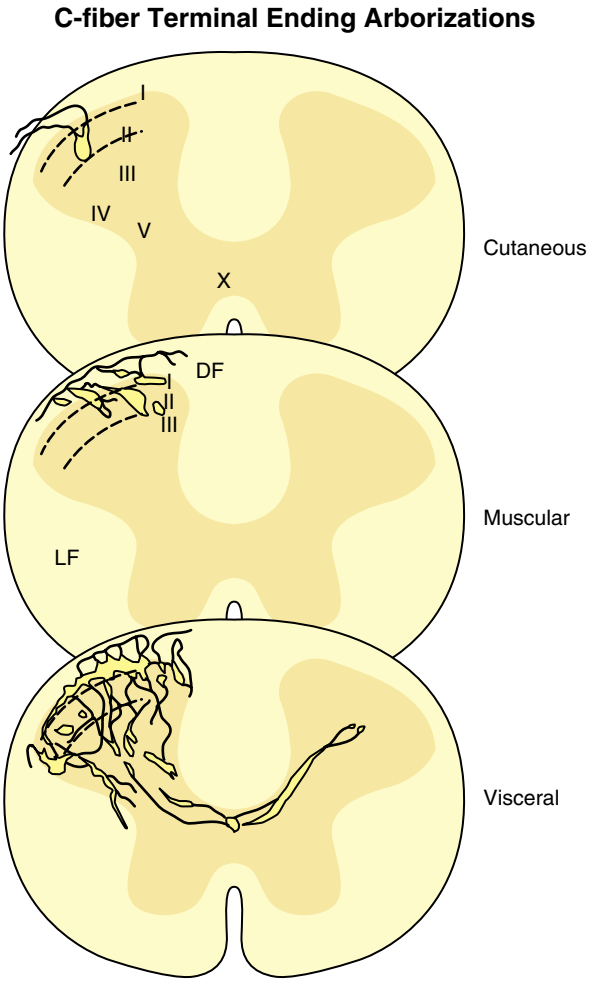
While peripheral nerves have both sensory and motor functions, all sensory afferent fibers, whether they innervate cutaneous, deep, vascular, or visceral tissue, separate from motor fibers near the spinal cord and join to form the dorsal root before entering the spinal cord on the dorsal surface (Fig. 8.3). Primary afferent fibers providing input from visceral structures and the vasculature travel along with the sympathetic efferent nerves. However, they pass directly through the sympathetic trunk to join other afferent fibers entering the dorsal horn of the spinal cord (Fig. 8.4). They remain silent unless provoked by inflammation or abnormal distension.

Cell Bodies in Dorsal Root Ganglia

The cell bodies of the nociceptive primary afferent nerve fibers lie just outside the spinal column clustered in the dorsal root ganglia (DRG). Nociceptive DRG neurons are small and medium sized but lie among the large dorsal root ganglion cells activated by touch, pressure, and vibration.[7,25,26] They extend their axons centrally to the spinal cord as dorsal roots. As in most central neuronal circuits, glutamate is the primary neurotransmitter substance in primary afferent nociceptors. Its action is modulated by neuropeptides co-released at their terminal endings and activation molecules. Calcitonin gene-related peptide (CGRP), SP, neurokinin A, galanin, and somatostatin are just a few examples of the many neuropeptides that provide



• **Figure 8.3** Nociceptive afferent nerve fibers have receptive free nerve endings in the dermal papillae of the skin and in the muscle, vasculature, and visceral structures. Nerves carrying nociceptive information travel with other somatic and autonomic motor axons, even passing through the autonomic ganglia, but have their cell bodies in the dorsal root ganglia located in the spinal vertebral column. The central axonal projection of afferent nerve fibers then passes through the dorsal root to innervate the spinal cord dorsal horn. Nociceptive information is relayed across at least one synapse in the dorsal horn to alert cells with projections to higher centers. The spinothalamic tract (*STT*) cells in the superficial dorsal horn send an axonal projection across the midline to travel in the lateral STT. STT cells in the deep dorsal horn send axons across the midline to ascend in the ventral white matter. STT cells bring information about both somatic and visceral pain to the thalamic levels. Post-synaptic dorsal column (*PSDC*) cells relay information about visceral pain through the ipsilateral dorsal column.



• **Figure 8.4** C-fiber terminal endings have been physiologically characterized and then filled with dye to reveal their terminal arborizations in the dorsal horn of the spinal cord. Examples of terminal arbors of axonal fibers with cutaneous, muscular, and visceral receptive fields are illustrated. The morphology of the cutaneous axonal ending would provide the anatomic substrate for precise point-to-point localization of a nociceptive insult on the cutaneous surface. Likewise, the diffuse widespread terminal arborization pattern of visceral afferent nerve fibers would account for the poor localization of visceral nociceptive sensation, which can be "referred" to other structures. Most visceral afferent nerve fibers innervate neurons that lie in the midline and some of the visceral fibers even cross the midline. The Roman numerals indicate Rexed's laminae. *DF*, Dorsal funiculus white mater; *LF*, lateral funiculus white matter.

neurogenic modulation and inflammation peripherally.[25,27] Modulatory neuropeptides produced in the DRG are transported quickly, both to the terminal endings in the periphery and to the spinal cord, and thus may not necessarily be evident in the cell body without experimental manipulations. The small satellite glia, the other primary component of the DRG, provide support but are capable of providing modulatory influences on the neurons that promote peripheral and central sensitization. The DRG, as well as afferent nerve endings both centrally and peripherally, are activated by pro-inflammatory mediators such as TNFα, IL-1, and IL-6.[28,29] Other activators include the small molecules adenosine, TRPV1, ATP, nitric oxide, and other reactive oxygen species.[30–34] All of these pro-inflammatory substances have been identified as being present at nerve terminal sites, in the DRG, and in the dorsal horn.

Transcriptomic profiling of single sensory ganglia neurons provides further functional classification diversity and molecular drug targets. As an example, ribonucleic acid (RNA) sequence data for visceral sensory neurons has been investigated.[35] Seven distinct subtypes of visceral sensory neurons of the splanchnic and pelvic sensory nerves retrogradely traced from their innervation of the colon have been distinguished using combined single-cell RNA sequencing, calcium imaging, qRT-PCR, and immunohistochemical validation as reviewed previously.[36] Five subtypes enter the thoracic level from the splanchnic nerve, and two almost exclusively from the pelvic nerve are located in the lumber five (L5) DRG. Like the distinct differences in somatic and visceral sensation, the molecular phenotype of visceral transient receptor potential channel (TRP)-sensitive mechanosensors differs from analogous somatosensory mechanosensors.[36] While both isolectin B4 positive (IB4+) and IB4- somatosensory neuron mechanoreceptor subtypes from naïve mice have similar broad tetrodotoxin (TTX)-resistant action potentials, proprioceptive neurons relaying position sense have TTX-sensitive, narrow action potentials.[37] Transcriptional profiling has revealed that these differences in firing characteristics can be attributed to the very different ion channel expression patterns of these neurons. Nociceptive neurons are highly enriched for Cacna2d1 (α2δ1) and Cacna2d2 (α2δ2), the pharmacologic targets of gabapentin and pregabalin.[38–40] Both IB4+ and IB4- somatosensory neurons express sodium ion channel Nav1.7, which, when congenitally absent in individuals, renders them without pain sensation and unprotected from injury.[41]

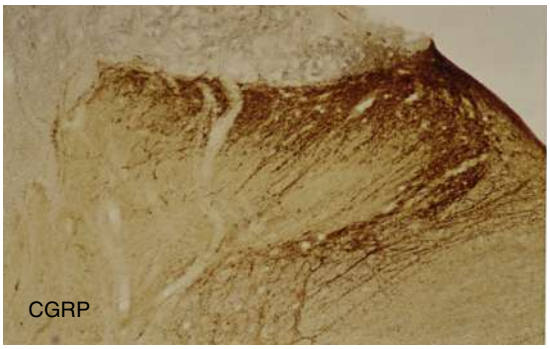
Spinal Cord and Spinal Trigeminal Nucleus

Nociceptor Terminations in the Spinal Cord Dorsal Horn

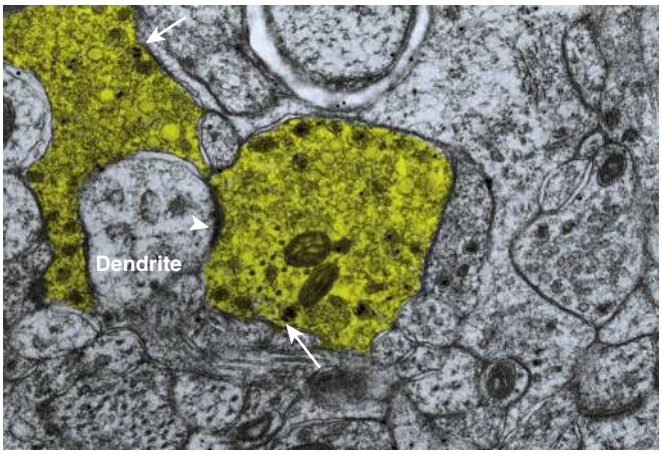
The afferent fibers enter the gray matter of the spinal cord through the dorsal root entry zone and primarily innervate regions of the spinal cord within the same or adjacent spinal segments matching that spinal nerve. The two major populations of small diameter primary afferent nerves carrying pain related information to the dorsal horn are classified as 1) peptidergic containing CGRP (Fig. 8.5)[42–44] and SP terminating in Lamina I-II_{outer}, and 2) nonpeptidergic neurons expressing P2X3 and binding IB4 terminating in Lamina II_{inner}.[45–47] Functional distinction between these nociceptors has been noted for their involvement in inflammatory and acute pain (IB4-), while the IB4+ neurons have more involvement in mechanical and chronic pain.[48–50] The IB4- neurons also express GDNF, TrkA, TRPV1, and other acid-sensing ion channels (ASIC) and have larger heat-evoked currents.[50–53] Neurons that are strongly IB4+ are C-nociceptor type with higher density of Nav1.9 voltage-gated TTX-resistant Na+ channel expression defining their longer action potential durations and rise times, slower conduction velocities, and negative membrane potentials.[47,51,54–57] A-δ low threshold mechanoreceptive neurons are weakly IB4+ or IB4-.[55]

Dorsal Horn Laminar Organization

The smaller myelinated and thinly unmyelinated axonal fibers carry information about temperature, and nociceptive input perceived as pain in humans enters the spinal cord segmentally through the dorsal roots. The fibers enter Lissauer's tract, then primarily innervate the superficial gray matter laminae I–II of the spinal cord where neuronal cell bodies and dendrites receive their



• **Figure 8.5** Calcitonin gene-related peptide (*CGRP*) is a good marker of the population of primary afferent nerve terminals innervating the dorsal horn.



• **Figure 8.6** Many afferent nerve terminals in the spinal cord dorsal horn terminate in irregular, scalloped endings filled with both clear and dense core vesicles containing neurotransmitter substances. The scalloped endings (*colored yellow*) are formed as the endings contact numerous small dendrites of spinal neurons, such as the one shown containing the arrowhead. The arrowhead is directed toward a synaptic contact. Several of the dense core vesicles illustrated (*arrows*) in the terminal endings contain dense gold particles indicating immunolocalization of calcitonin gene-related peptide.

arborized synaptic endings (Figs. 8.3 and 8.4).[58] The afferent fibers may also ascend rostrally or descend caudally through Lissauer's tract for a few spinal segments. For example, CGRP fibers extend extensive fiber terminations up and down the superficial spinal cord dorsal horn through as many as six spinal levels and can even cross the midline in small numbers.[42,59] Numerous other neuropeptides have been localized in the dorsal horn terminals and neurons.[27] Visceral afferents are rich in vasoactive intestinal polypeptide (VIP), bombesin, CGRP, and SP[8,25] and would account for some of the population of these peptides in the deep dorsal horn laminae. Other neurotransmitters and neuromodulators are discussed more thoroughly in Chapter 9.

The outer marginal layer or lamina I of the spinal cord contains nets of spiny dendrites of cells that are longitudinally arranged along the length of the cord. Somatic nociceptor C-fiber afferent endings are distributed mainly to laminae I and II in the same and adjacent segments. In contrast, visceral C-fiber afferents can extend for more than five segments before they terminate and are widely distributed in laminae I, II, V, and X ipsilaterally and in laminae V and X contralaterally (Fig. 8.4).[60,62] In addition to the afferent endings, fiber terminations of the descending pathways and the local interneurons also heavily innervate the superficial dorsal horn laminae I–II, adding to the dense crescent of terminal endings observed when stained immunocytochemically for many neurotransmitters and receptors. Cutaneous Aδ mechanical nociceptors terminate in the ipsilateral laminae I and V, and they may also have endings in lamina X and the contralateral dorsal horn.[61,62]

Primary Afferent Endings Contain Glutamate

Primary afferent endings in the spinal cord dorsal horn contain small, round, clear glutamate containing vesicles released upon nerve activation for synaptic transmission and relay of nociceptive information to spinal cord neurons.[44] The large, glomerular type afferent endings typically contain large, dense cored vesicles containing peptides[63] (Fig. 8.6). CGRP receptors on post-synaptic membranes of spinothalamic tract neurons are found opposite glomerular, elongated, and dome-shaped synaptic endings in the superficial dorsal horn.[42] In high activation states such as after tissue damage, increased release of glutamate further increases the activation of dorsal horn neurons as it does in other sites of neural integration. The increased release is accompanied by the release of small molecule modulatory peptides expressed by primary afferent neurons, including SP, CGRP, VIP, and cholecystokinin (CCK).[25–27,64] These modulators, along with cytokines (TNFα, IL-1β, IL-6) released from adjacent microglia and astrocytes in the spinal cord, generate central sensitization in the case of intense and/or prolonged nociceptive stimulation.[28,65]

Pre-synaptic Inhibition, Primary Afferent Depolarization, and Dorsal Root Reflexes

When afferent nerve endings are activated persistently after an injury, increased release of glutamate and other excitatory amino acids in the dorsal horn activates spinal cord interneurons.[66–68] The post-synaptic activation results in the increased firing of GABAergic inhibitory interneurons as well as the firing of excitatory interneurons. The gamma aminobutyric acid (GABA) hyperpolarizes the neuronal membrane that dampens incoming afferent firing. Pre-synaptic inhibition also occurs as the excessive glutamate activates autoreceptors on the afferent endings.[69] The depolarized membrane also causes the inactivation of voltage-gated calcium channels, preventing calcium influx at the synapse. The net result of pre-synaptic inhibition is reduced amplitude of the action potential as it invades pre-synaptic terminals. This results in less calcium influx and therefore less transmitter release. However, as the pre-synaptic inhibition continues, other changes in the inhibitory control process result in prolonged membrane hyperpolarization and chloride conductance that can actually depolarize the afferent nerve endings themselves. This occurs because of the activation of $GABA_A$ receptors that open Cl^- channels allowing chloride to enter the cell passively as it follows the chloride equilibrium gradient. Eventually, this will result in Cl^- efflux as the equilibrium potential is exceeded, resulting in depolarization of the afferent terminal. This process is referred to as primary afferent depolarization.[70] The depolarization can be blocked by antagonists of $GABA_A$ receptors. These findings and the initial work by John Eccles on pre-synaptic inhibition have since been extended in various ways. For example, it was later explained that with persisting afferent nerve activation, the potassium-chloride co-transporter (N^+-K^+-$2Cl^-$, NKCC1) becomes insufficient to remove the influx of chloride ions from the afferent terminals. When the intercellular

chloride ion concentration exceeds the equilibrium potential, a reversal occurs, and there is an efflux of chloride ions. After that, GABA has a depolarization effect.[71–73] Another contributor proposed is the increase in the extracellular concentration of K^+ following neural activity.[74]

Activation of nociceptive neurons resulting in primary afferent depolarization of the dorsal horn nerve ending initiates action potentials in the central afferent terminals. The action potentials generated travel back out the afferent nerve toward the periphery, where they have been recorded in A-β, A-δ, and C-fibers.[75–77] These "dorsal root reflexes" release neurotransmitters peripherally into the damaged tissue, such as glutamate and peptides, contributing to the increase in inflammation and peripheral blood flow, but it can be blocked centrally by $GABA_A$ and non-NMDA antagonists.[76–79] Likewise, the action potentials contribute further to the increased excitatory transmitter release in the dorsal horn. These events set up a reverberating positive feedback loop, amplifying nociceptive input and increasing both peripheral and central sensitization that can promote the establishment of chronic pain if it continues.

Spinal Interneurons

Most of the spinal cord neurons are interneurons (~90%).[80] The gray matter at the core of the spinal cord dorsal horn that receives sensory nerve terminations is comprised of excitatory and inhibitory integrative interneurons forming the first tier of sensory information processing, integration, and modulation of sensory inputs arising from the peripheral or internal environment. Spinal interneurons also receive input from other interneurons and descending pathways that together impact and integrate their responses.

Functional Somatotopy and Spinal Interneurons

Noxious input relayed by the primary afferent fibers is received by the dendritic arbors of neurons in the dorsal horn gray matter of the spinal cord. The gray matter is a matrix of synaptic terminations, neurons, and glial cells subdivided topographically as 10 laminae by Rexed based on histologic appearance (Figs. 8.4 and 8.7).[81,82] The site of afferent fiber type terminations centrally in spinal gray matter laminae is relevant to function. The importance of the laminar organization has been upheld by other phenotypic findings, including chemogenetic,[83] optigenetic,[84,85] and gene expression patterns.[86–89] Prominent among overrepresented genes in spinal neurons are transcription factors (30%–38%) and neuropeptides (24%–26%) relevant to a specific function.[90]

Excitatory neurons utilize glutamate neurotransmission (60%–70%) and inhibitory interneurons (30%–40%), GABA, and glycine.[58] Fifteen types of excitatory and 15 types of inhibitory interneurons have been identified using single-cell RNA sequencing in the mouse spinal cord.[88] Validated by spatial transcriptomics, this laminar distribution report classified heat and cold sensitive excitatory and inhibitory neuronal sets. In addition to glutamate, GABA, and glycine, interneurons contain many neuroactive substances that are presumably neurotransmitters or modulators involved in nociceptive processing by the local interneuronal circuits of the dorsal horn. These substances include adenosine, choline acetyltransferase, cholecystokinin, corticotropin releasing factor, dynorphin, enkephalin, galanin, neurokinin B, neuropeptide Y, neurotensin, protein kinase C γ, somatostatin, SP, and thyrotropin-releasing hormone.[8,87] Additional information on the molecular content is described in Chapter 9.

Excitatory interneurons predominate in the dorsal horn, although lamina II or the substantia gelatinosa contains both excitatory and inhibitory interneurons that modulate projection neurons. Two non-overlapping populations have been identified characterized by either their content of gastrin-releasing peptide (GRP) or SP (radial neurons with many dendrites).[88] The SP neurons generally show delayed firing and respond to noradrenaline and serotonin with an outward current under voltage clamp conditions, suggesting that they respond to descending monoamine modulatory input, but they have no response to A-δ opioid receptor agonist. The GRP interneurons do not respond to 5-HT, or NA, but respond with an inhibitory outward current to μ-opioid receptor agonist DAMGO under voltage clamp conditions. They do not respond to δ or κ agonists. The GRP interneurons have local intersegmental connectivity. Typical of lamina II are the large glomerular synaptic complexes sometimes referred to as scalloped primary afferent endings that contact multiple dendrites of dorsal horn cells simultaneously (Fig. 8.6).[7,92–95] The terminals contain large dense core vesicles, which are identified as neuropeptide-containing, with CGRP in particular. Dorsal horn protein kinase C gamma (PKCγ) containing excitatory interneurons (30%) with islet-like morphology and abundant spines have been characterized by delayed firing patterns and receive synaptic inputs from both Aδ and C low threshold mechanoreceptors.[87] Six other excitatory and four inhibitory interneurons receiving low threshold mechanoreceptor information were identified using genetic tools in that study.

The GABA inhibitory interneurons take the form of stalked (limiting) cells and the inhibitory containing islet (central cells) interneurons.[83,96] GABA interneurons contain parvalbumin (70%), and those found in laminae I and III can also contain another inhibitory amino acid, glycine,[87,97–99] with dendrites extending both dorsally into lamina I and ventrally into deeper laminae of the dorsal horn. The orientation of intralaminar connectivity among the excitatory dorsal horn interneurons in lamina II is extensive in the rostrocaudal plane compared to the inhibitory interneuronal connectivity, and both have limited dendritic spread in the mediolateral plane.[100] The central, radial, and islet cell populations receive extensive input almost entirely from within lamina II, including substantial input from both IIo and IIi. The vertical cell population receives additional input from the deep dorsal horn lamina III–IV and has been speculated to be highly modifiable in states of continued nociceptive activation.

Role of Spinal Interneurons in Gate Theory Spinal Inhibition

The many interneurons in the spinal cord circuitry are also highly involved in spinal modulation that decreases the impact of noxious input. Inhibition of spinal transmission by weak mechanical stimulation can occur either through activation of segmental or supraspinal circuitries. The events that can inhibit nociceptive transmission can occur by reducing neurotransmitter release from nociceptor terminals. While physiologists have conveniently explained "surround" type inhibition of dorsal horn synaptic transmission in terms of dorsal horn axo-axonic synaptic transmission, only a few anatomic figures of this type have been described for the dorsal horn.[98,101,102] Rather, the anatomic arrangement of synapses for the Gate Theory of Pain proposed by Melzack and Wall[103] is likely mediated through axodendritic arrangements of CGRP primary afferent terminals innervating the dendrites of GABA interneurons in lamina II and reciprocal interactions that

are difficult to image reliably. Fine myelinated and unmyelinated CGRP labeled afferent fibers have been observed synapsing with GABAergic dendritic profiles (islet cells),[102] which have also been shown to contain glycine.[98] GABA interneurons are uniquely qualified to provide the "pre-synaptic" inhibition of nociceptive input either through contacts provided by their dendrites back onto CGRP primary afferent endings or through axonal contacts back onto other dorsal horn neurons.[103] Other inhibitory neurons in the dorsal horn contain dynorphin and glycine. Similarly, an interposed excitatory interneuron, such as one containing glutamate, would provide an excitatory boost to spinal nociceptive processing. Interestingly, neurons in lamina II, the substantia gelatinosa, do not respond to the release of SP since they lack NK_1 (SP) receptors.[104] The SP terminal endings are located on nociceptive projection cells in both lamina I and the deep dorsal horn, including lamina I cells with NK1 receptors that rapidly internalize the receptors upon nociceptive stimulation.[105,106]

Role of Interneurons in Central Sensitization and Allodynia

The interneurons in the dorsal horn have been found to be highly involved in the activation of central sensitization when the nociceptive pathway is exposed to repeated noxious stimuli.[107–110] Dysregulation of the balance of excitatory and inhibitory interneurons results in sustained nociceptive transmission to higher brain levels.[107] Further discussion is provided below since glia are intimately involved in this process.

While signals from nociceptors are relayed across at least one synapse to activate spinal neurons prior to arriving at higher brain regions, input for non-noxious tactile discriminative sensory information (tactile, pressure, vibratory sense) is relayed directly to the dorsal column nuclei in the brainstem (Figs. 8.1 and 8.3). However, in states of intense or prolonged overactivation, the large myelinated primary afferent fiber collateral input to the dorsal horn becomes involved in nociceptive processing.[111] Their collateral input activates deep dorsal horn laminae III–IV neurons that then become sensitized in conditions of central disinhibition.[112] The percentage of superficial dorsal horn interneurons that receive polysynaptic A-β input is normally relatively low but can be increased by inhibitory transmitter blockade.[112] Increase in A-β input to the superficial dorsal horn in animal models of inflammatory or neuropathic pain hypersensitivity has also been reported.[113–116] This contributes to hypersensitivity, including thermal and mechanical allodynia.

Role of Glia in Central Sensitization, Allodynia, and Paradoxical GABAergic Excitation

Activation of spinal cord microglia (one to three days) and astrocytes (one to two weeks) after nerve injury plays an important role in the establishment and maintenance of neuropathic pain.[65,117–119] Microglia in the CNS have an innate immune function sensing damage, assuming a reactive morphology, and upregulating to secrete pro- and anti-inflammatory cytokines. After an injury, release of microglial BDNF and BDNF-TrkB signaling downregulates neuronal chloride transporter KCC2, resulting in a depolarizing shift in neuronal Cl- reversal potential. This increases the membrane potential such that inhibition is impaired and allodynia results.[73,120–123] Thus while chloride transporter KCC2 activity extrudes intracellular chloride to maintain Cl- membrane electrochemical gradient necessary for $GABA_A$ and glycine interneuronal inhibition, disruption of the inhibition and upregulation of facilitatory $GABA_B$ contributes to central sensitization.[71,72,123–126] Importantly, a second chloride transporter NKCC1 in lamina I–II peptidergic nerve terminals contacts astrocytes.[127] When activity in primary afferents is upregulated following an inflammatory insult, excessive GABA-ergic depolarization is produced in primary afferent terminals, leading to paradoxical excitation and cross excitation between low and high threshold afferents.[111]

The role of specific molecular targets upregulated in glia is also under investigation. For example, spinal cord astrocytes are activated by microglial-derived C1q in the late phase after somatic and trigeminal nerve injuries.[128] Upregulated TRAF6 has been shown to maintain neuropathic pain by integrating TNFα and IL-1β signaling and activating the JNK/CCL2 pathway in astrocytes.[129]

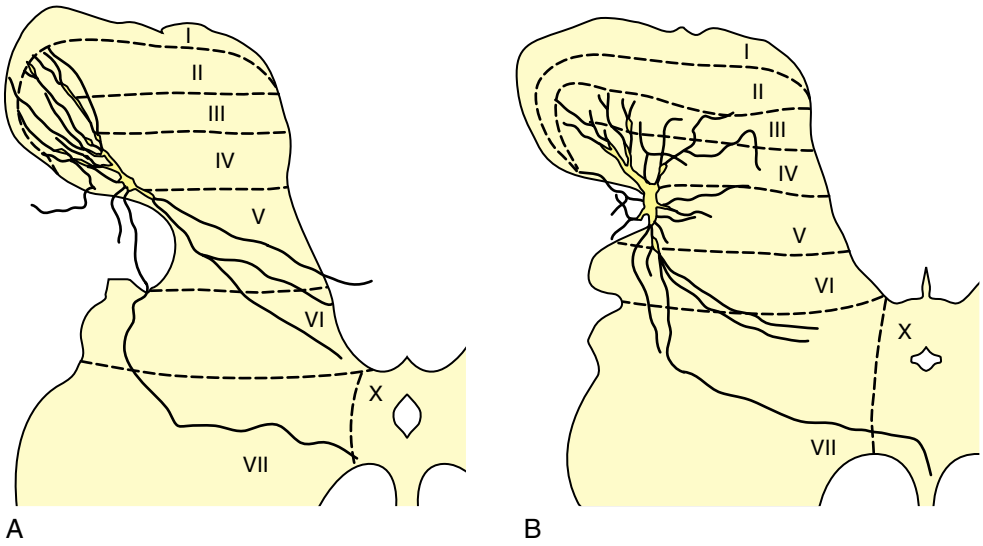
Thus nociceptive information entering the spinal cord dorsal horn is modulated by both excitatory and inhibitory neuronal and glial influences at the level of the spinal cord, prior to being relayed by projection neurons to higher centers. Modulation occurring after an injury or disease influences the local interneuronal circuitry and the circuitry activated by the projection neurons that influence brainstem modulatory input and higher brain pain circuitry.

Ascending Pain Pathways

Morphology of Projection Neurons

Several types of projection neurons in lamina I that send their axon rostrally to the brainstem have been described by Lima and Coimbra.[130–133] These cell types include fusiform (spindle-shaped), multipolar, flattened, and pyramidal neurons. Different subsets of these cells project their axons to the nucleus of the solitary tract, to the dorsal and lateral reticular nuclei in the medulla, pons and midbrain, and the thalamus. Neurons of the same morphologic type express SP, enkephalin, dynorphin, or GABA,[134] although some of the cells may have been interneurons. Three morphologic types of lamina I spinothalamic tract (STT) cells have been described in cats and monkeys: fusiform, pyramidal, and multipolar.[135,136] Evidence has been provided that the fusiform and multipolar STT cells are nociceptive, whereas the pyramidal STT cells are thermoreceptive.[137] Consistent with this, most fusiform and multipolar lamina I STT neurons express NK1 receptors, and most pyramidal STT cells do not.[104,138]

The projection cells found in the deeper laminae of the dorsal horn are typically located laterally in the dorsal horn. They are large, multipolar neurons with extensive dendritic arbors to receive numerous inputs and can thus convey highly integrated information to the thalamus. The dendrites of the deep projection cells tend to arborize radially in the spinal cord dorsal horn, in contrast to the lamina I projection cells whose dendrites are longitudinally distributed along the dorsal surface of the spinal cord gray matter so that they are barely visible in the coronal plane. A radial dendrite arrangement provides for the integration of the convergent input encoded by the STT cells in the deeper laminae instead of the superficial projection neurons situated to have ready access to specific incoming nociceptive and thermal input directly via the afferent nerve fibers. Some STT cells in deeper laminae do have dendrites that extend dorsally into lamina I and II (Fig. 8.7). These STT cells receive direct synaptic connections from the terminals of nociceptors ending in the superficial dorsal horn and are particularly responsive to high



• **Figure 8.7** Spinal cord cells that were physiologically characterized were filled with a stainable dye and reconstructed over many spinal cord slices to provide details of their dendritic arborization. The cell in A was characterized as a high threshold cell since it responded to intense stimulation in the digit of the hind limb. The cell body is situated in lamina IV, and its dendrites extend into all laminae. Dendrites extend almost a millimeter in the rostrocaudal direction. The axon bifurcates to cross the midline ventrally in lamina X, passing into the dorsal column. The cell in B was characterized as a "wide dynamic range cell" responding to a broader range of cutaneous input. The cell body is situated in lamina V, and its dendrites extend radially in all directions, including 1.2 mm in the rostrocaudal direction. The axon is seen crossing the midline in lamina X. The *dashed lines and Roman numerals* indicate Rexed's laminae.

threshold input.[7,139–141] Other STT cells identified as "wide dynamic range" cells respond to various mechanical, thermal, and nociceptive inputs. They have dendrites that extend chiefly in the ventral direction and receive convergent input from afferents supplying both deep somatic and visceral structures.

The spinothalamic tract and interneuronal cells in the dorsal horn express the early intermediate gene activation marker, c-Fos, with brief nociceptive stimulation in laminae I, IV, and V, whereas sustained nociceptive stimulation is needed to activate c-Fos in deeper laminae III, V, VII, and X, as in models of joint and visceral inflammation.[142,143] Some contacts on retrogradely labeled STT projection neurons contain peptides, such as SP, enkephalin, dynorphin, or VIP.[144,145] The dorsally directed dendrites of many deep dorsal horn neurons contain NK_1 (SP) receptors,[143] and these are internalized following presumably painful stimulation occurring during inflammation.[135] Lamina X STT cells have been shown to contain CCK, bombesin, and/or galanin.[146,147] Synapses found on the cell bodies of non-human primate and rat STT neurons of deep layers of the dorsal horn contain glutamate, GABA, glycine, SP, CGRP, vasopressin, norepinephrine, or serotonin.[102,105,141,148,154] Electrophysiologically characterized primate STT cell bodies with projections to the ventroposterolateral thalamus are glutamatergic. They are contacted by both excitatory (50%) and inhibitory (30%) terminals for direct impact integrative processing.[102,141] These ultrastructural studies have revealed post-synaptic localization of glutamate receptor subunits NMDA R1, AMPA GluR1, and GluR2/3, and metabotropic mGluR1.[153,154] The glutamate NMDA R1, mGluR2/3, and AMPA Glu R2/3 receptor subunits were localized pre-synaptically on the terminals contacting the identified STT neurons.

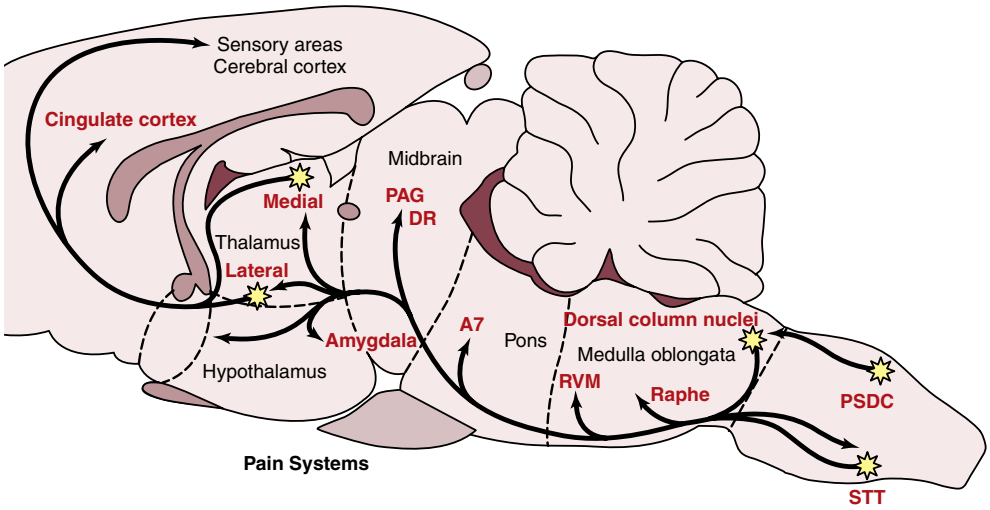
Ascending Pain Pathways

Medial Versus Lateral Pain Pathway Designation

The ascending pathways activated by noxious input are sometimes distinguished as medial and lateral pain pathways. An interesting hypothesis is that medial and lateral pain pathways provide affective and epicritic (discriminative) pain sensations, respectively. The ventrolateral spinothalamic tract clearly provides information for specific discrimination of pain and temperature, somatotopic localization, and quality and intensity coding of cutaneous pain. Some of the pathways in unique positions to assume a role in affective pain awareness include the spinoamygdalar pathway, the spinal pathways relaying visceral pain through the post-synaptic medial dorsal column route, and ventromedial projections to midline structures, including the rostral ventromedial medulla, periaqueductal gray, hypothalamus, and centrolateral and medial thalamus. Some of the non-overlapping but parallel medial and lateral ascending pathways carrying information to brain centers responsive to pain are described below.

Lateral Pain Pathways

Spinothalamic Tracts. The main lateral pain pathway is the well-known spinothalamic tract that transmits site-specific (discriminative) information about the location, quality, and intensity of the noxious input to the lateral thalamus. Thalamic neurons then relay the information to the SI, SII somatosensory cortex. The spinothalamic tract neurons send ascending axonal fiber projections across the spinal cord midline cord in the anterior white commissure ventral to the central canal. The STT axons in the deep dorsal horn (laminae IV–VII, X) ascend in the contralateral (opposite side) ventrolateral white matter of the spinal cord and brainstem (Figs. 8.1, 8.8 and 8.9).[155] The axons of STT cells terminate laterally in the posterior ventrobasal thalamic complex (ventral posterolateral, ventral posterior inferior) or medially in the medial and intralaminar thalamus (subparafascicular and central lateral). The thalamus is the main integration site of sensory information that is then provided to the somatosensory cortex. Noxious tactile information from the same body region converges upon the same thalamic neurons. The point-to-point reception of information in the lateral thalamus provides somatotopic encoding for specific localization of the input onto the cortical representation of the specific body region.[156] This provides the ability to precisely locate the origin of the nociceptive input.



• **Figure 8.8** Pain systems include the spinothalamic tract and the post-synaptic dorsal column pathways. These parallel pain systems ascending from the spinal cord converge to course through the brainstem as the spinothalamic tract and the medial lemniscus. Although the primary termination site for sensory integration is the thalamus, abundant collateral terminations are provided to integration sites throughout the brainstem. The ventral posterolateral nucleus of the thalamus is the principal somatosensory relay for information provided to the sensory areas of the cerebral cortex for localization of pain sensation. The medial and intermediate portions of the thalamus project to the anterior cingulate and frontal cortex, respectively, and provide input relevant to the affective responses to pain. Autonomic adjustments occur in response to the input provided to the hypothalamus. *A7*, Noradrenergic cell group; *DR*, dorsal raphe; *PAG*, periaqueductal gray; *PSDC*, post-synaptic dorsal column cell; *RVM*, rostral ventromedial medulla; *STT,* spinothalamic tract cell.

The STT cells receiving noxious temperature input are largely situated in lamina I.[157] Lamina I STT neurons send their axonal projections in the lateral white matter to terminate in the posterior part of the ventral medial nucleus of the thalamus and in the ventral posterior and medial dorsal nuclei. Early electrophysiologic studies reported parallel processing of nociceptive inputs in the cortex arising from the ventrobasal thalamus to the sensory (SI, II), cingulate, and insular cortex. This includes somatosensory and visceral sensory input from ventral posterolateral (VPL) and centrolateral (CL) thalamic nuclei, respectively, and oral/tooth pulp input from the ventral posteromedial nuclei (VPM) of the thalamus.[158–160]

Collateral branching of the spinothalamic tract innervates many sensory processing regions as it ascends, including the dorsal column nuclei, dorsal and ventral medullary reticular formation, dorsolateral pontine locus coeruleus/parabrachial region, midbrain periaqueductal gray, anterior pretectal nucleus, hypothalamus, and amygdala, as has been described and reviewed previously (Figs. 8.1, 8.8 and 8.9).[161–166] While much of the initial information about pain anatomy and function was derived from animal studies, clear visualization of activation in cortical sites is now available with functional magnetic resonance imaging (fMRI) imaging and is reviewed in a later chapter.[167,168]

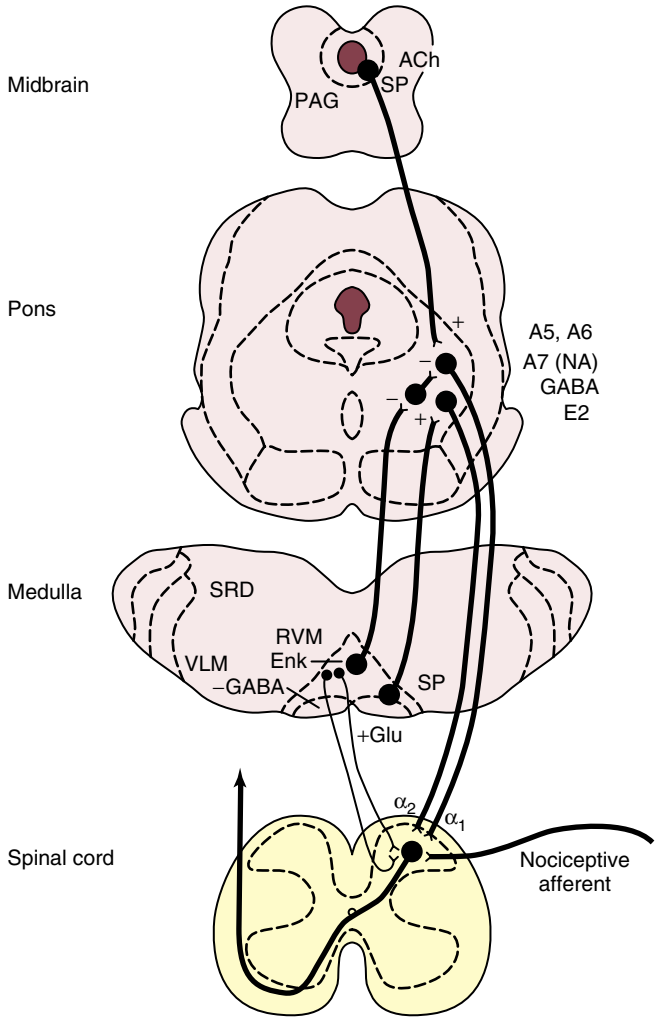
Spinoreticular pathways. Many projection axons from the spinal cord also provide direct and collateral innervation to the brainstem regions involved in pain related activities, including descending modulation of pain, autonomic responsiveness, alerting response, escape responses, and limbic and cortical activation. Collectively, these neurons are referred to as the spinoreticular system (Fig. 8.1, 8.8).[162,169–171] These integrative regions modulate and balance excitatory and inhibitory neuronal influences on nociception through reciprocal higher brain connectivity that ultimately determines the pain state.

A dorsal spinomedullary pathway arises from cells in laminae I, IV, and X to terminate bilaterally in the subnucleus reticularis dorsalis (SRD) of the dorsal medullary reticular formation, which is located just ventral to the cuneate and solitary nuclei of the dorsal medulla.[164,170] This nucleus is a brainstem site active in balancing descending inhibition and facilitation of nociceptive processes. The diffuse noxious inhibitory controls (DNIC) inhibiting wide dynamic range neurons in the spinal cord and competing with afferent input are dependent on a supraspinal loop through the SRD and a descending pathway.[170] Projections from this region innervate the contralateral somatosensory, motor, limbic, and insular cortex, and the periaqueductal gray (PAG), pons, cerebellum, trigeminal, and other brainstem nuclei.[172] Connections to the anterior cingulate gyrus participate in the descending facilitatory modulation of pain.[173]

Medial Pain Pathways

The medial pain system transmits nociceptive information to the midline brainstem, hypothalamus, amygdala, and the medial and intralaminar thalamus to regions organizing responses to pain.[174–178] Innervation of the hypothalamus and limbic structures, including the anterior cingulate cortex, activates affective, motivational, and autonomic responses to pain. Medial pain pathways include the spinoamygdalar, spinohypothalamic, medial spinothalamic, spinoreticular, and connections to the anterior cingulate, prefrontal, and insular limbic cortices.[171–174] Some of these axons include neurons in lamina X known to transmit visceral information.[175–178]

Anterograde and retrograde tract tracing studies demonstrate other first and second order pathways ascending on the same side or crossing to the opposite side white matter. Associated ascending spinal cord white matter projections described include the spinoreticular, spinoparabrachial, spinomesencephlic, spinohypothalamic, spinothalamic, spinoamygdalar, spinoinsular, and other spinolimbic tracts.[163–174] This includes innervation of the medullary subnucleus reticularis attributed to provide DNIC[164,170] and innervation of the medial thalamic nuclei, habenula, and insular cortex providing information about noxious visceral inputs.[175–178]



• **Figure 8.9** Multiple integration sites in the brainstem receive nociceptive input from the ascending pain systems. Complex brainstem circuitry provides both descending inhibitory and excitatory alterations of nociceptive responses at the level of the spinal cord. Cells are situated side by side in the rostral ventromedial medulla (*RVM*) that impose either excitatory or inhibitory influence. Cells in the RVM are both serotonergic (5-hydroxytryptamine) and nonserotonergic. They provide both a direct descending pathway to the spinal cord and a major input to the dorsolateral pons. The A5 to A7 noradrenergic (*NA*) cell groups in the dorsolateral pons provide major inhibitory feedback to the spinal cord. The PAG and the anterior pretectal nuclei provide inhibitory input to the spinal cord through connections with descending pathways from the dorsolateral pons. Specific neurotransmitters within brainstem regions are noted, as are specific receptors having an impact on nociception in the spinal cord dorsal horn. *ACh*, Acetylcholine; *E2*, estrogen receptor 2; *Enk*, enkephalin; *GABA*, γ-aminobutyric acid; *Glu*, glutamate; *SRD*, subnucleus reticularis dorsalis; *SP*, substance P; *VLM*, ventrolateral medulla.

Early electrophysiologic studies have reported that nociceptive inputs from the ventrobasal thalamus to the sensory (SI, II) cortex are paralleled by axonal projections to the limbic cingulate and insular cortices. This includes somatosensory and visceral sensory input from ventral posterolateral (VPL), medial, parafascicular, and centrolateral (CL) thalamic nuclei, and oral/ tooth pulp input from the ventral posteromedial nuclei (VPM) of the thalamus.[159,178–180] While much of the initial information about pain anatomy and function was derived from animal studies, clear visualization of activation and parallel processing in cortical sites is now available with fMRI imaging[168] and will be reviewed in a later chapter in this volume.

Post-synaptic dorsal column pathway. The spinal cord dorsal column midline contains less well studied ascending axons of the post-synaptic dorsal column neurons. These projection neurons are responsive to noxious visceral input. The axons are situated medial to the dorsal column ascending primary afferent neuronal axons relaying touch, pressure, and vibratory sensation. The cell bodies of many of these neurons are located in laminae III and IV[181] but are also described for lamina X.[176,177,181–183] Many excitatory interneurons near the post-synaptic dorsal column cells (30%) receive protein kinase C γ low threshold C-fiber mechanoreceptor synaptic input.[87] The neurons send a direct projection uncrossed to the caudal dorsal column nuclei in the dorsal medial medulla.[165,176,177,186] Sacral lamina X post-synaptic dorsal column neurons have axons traveling nearest to the dorsal column midline septum to terminate in the gracile nucleus. Axons arising from the thoracic spinal levels travel near the intermediate septum of the dorsal column and terminate in both the gracile and cuneate nuclei. The information is presumed to then travel with the crossed medial lemniscal fibers to the thalamus. Lamina X post-synaptic dorsal column neurons with axons transmitting visceral nociceptive information to the thalamus converge on some of the same thalamic cells receiving nociceptive information from the skin and other somatic structures (Fig. 8.1, 8.7).[175,180,183] Visceral only input can also be recorded in the centrolateral intralaminar nucleus of the thalamus.[177,186]

Spinohypothalamic, Limbic, and Cortical Connections. Pain is often accompanied by motivational-affective responses, including suffering, anxiety, increased attention and arousal, increased heart rate and blood pressure, as well as by changes in endocrine and autonomic responses. The neural structures and the pathways that relay these changes parallel those relaying information localizing the source of the noxious input on the body map but escape awareness in most instances.[178] Centrolateral and medial thalamic projections to the anterior cingulate and frontal cortices, respectively, have been described.[187,193] Their thalamic connections to the somatosensory (SI, SII) cortex and other cortical sites are less well studied.

Spinohypothalamic and spinoamygdalar pathways initially described are involved in autonomic and affective responses to pain.[172,188,189] Ascending axonal projections of these pathways arise primarily from the spinal cord laminae I and X), as well as from the lateral reticulated region of the spinal cord.[190–192] Synaptic contact is made in the lateral hypothalamus (LH) and the central nucleus of the amygdala (CA). Both of these regions are also involved in antinociceptive actions, as well as autonomic and affective responses to nociceptive input through connections with the medial thalamus and with other parts of the limbic system.

Spinal projections to the ventrolateral medulla are conveniently located to relay to the paraventricular nucleus of the hypothalamus,[166,189] amygdala,[167] and the medial preoptic region.[166,167,172,189,192] Ascending axonal projections of these pathways arise primarily from the spinal cord laminae I and deep spinal laminae (VII, VIII, and X).[160] The direct route to the medial thalamus, amygdala, and the spino-parabrachial-amygdala pathways are clearly involved.[187,188] A spino-reticulo-thalamo-cortical pathway was originally proposed as a projection to the forebrain relaying information about painful input, presumably for subjective interpretation based on known anatomical projections

of the reticular formation to higher brain centers.[195] Relays to the insular cortical structures have also been described as the "interoception" cortex receiving visceral input from all over the body.[196,197]

Evidence from imaging in patients with longitudinal back pain concludes that the plasticity of corticolimbic anatomic neuroanatomic features rather than the somatosensory pain circuitry contributes to the risk of chronic pain. Factors such as increased white matter connectivity and functional connections within the dorsal medial prefrontal cortex-amygdala-accumbens circuit, small amygdalar volume, and opioid gene polymorphisms contribute in these regions rich in opioid receptors.[198–200]

Trigeminal System. An important feature unique to trigeminal circuitry includes its close proximity to brain structures.[201,202] Information from the face pain travels via trigeminal primary afferents through the TG to synapse in the brainstem medullary dorsal horn as well as to directly innervate the parabrachial complex.[202] Thus the trigeminal innervation of the lateral parabrachial nucleus has more direct connectivity with the limbic system via one synapse while the spinal input crosses two synapses. Optogenetic activation of the trigeminal monosynaptic connectivity has been shown to induce escape and avoidance behavior.[202] Human study participants report increased fear after noxious facial stimulation compared to similar noxious stimulation of the hand.[203] Secondary axons ascend via the trigeminothalamic and parabrachio-amygdaloid tracts to the ventromedial thalamus and amygdala, respectively, then relay to several cortical and subcortical regions including primary and secondary somatosensory cortices, insula basal ganglia, anterior cingulate cortex (ACC), and limbic circuitry.[204,205] Nociceptive information relayed via the basal ganglia is transmitted to the prefrontal cortex and back to the amygdala.

Modulation of Pain

Ascending Modulation of Pain

Major ascending axonal projections relaying information about pain pass laterally through the brainstem but have collateral terminations in the reticular formation of the ventrolateral medulla (VLM), the rostral ventromedial medulla (nucleus gigantocellularus pars alpha and nucleus raphe magnus), and other sites known to modulate pain.[132,133,170,174] The collateral innervation of the monoamine cell groups are prominent in providing descending modulation. The midline raphe nuclei containing serotonergic and non-serotonergic neurons with descending projections to the spinal cord have been particularly well studied[124] and are reviewed in another chapter in this volume.

The spinal ascending pathways also traverse brainstem regions and have direct synaptic contact with catecholaminergic neurons, including the C1, A1, and A2 regions of the medulla and the A5, A6 (locus coeruleus), and A7 (subcoeruleus) neurons of the pons.[165] The catecholaminergic neurons of the brainstem are involved in diverse functions, including modulation of pain, stress responses, arousal, and learning. Connectivity is described among the ventromedial medulla and the catecholamine cells of the pons,[206,207] and the anterior cingulate gyrus,[173] as well as between brainstem catecholaminergic cells and the thalamus,[75] and ACC.[208] These interconnecting networks assist in the coordination of descending and facilitatory influences on pain perception and autonomic, affective, and stress responses.

Parabrachial Nuclei

Axonal collaterals of the ascending spinal projection neurons terminate in the parabrachial region. Small injections of retrograde tracer in the parabrachial nucleus confirm that the parabrachial nucleus receives projections primarily from lamina I nociceptive neurons.[208,209] The spino-parabrachial-amygdala pathways are clearly involved in descending inhibition, central pain, and emotional responses to chronic pain.[193–195]

Interestingly, high frequency stimulation inducing long term potentiation is described only for C-fiber synapses onto spinal lamina I neurons expressing neurokinin1 synapses with projections to the parabrachial nucleus.[209] The parabrachial nucleus projects directly to the PAG, amygdala, and ventrobasal thalamus.[210] Involvement in visceral nociceptive processing has also been reported for the parabrachial nucleus.[211] Direct trigeminal nerve innervation of the parabrachial nucleus is described as providing a route for direct access for orofacial nociceptive input to the amygdala.[202]

Periaqueductal Grey

Ascending pathways relaying nociceptive information are influential in the activation of the PAG, pontine noradrenergic cell groups, and midline midbrain reticular formation.[174,213–215] Direct neuronal projections from the central region of the spinal cord to midline brainstem nuclei, including the rostral ventromedial nucleus of the medulla and the midbrain PAG and raphe magnus, have been described as well.[177]

Anterior Pretectal Nucleus

Another termination site innervated directly by ascending pathways from the spinal cord and from the dorsal column nuclei is the anterior pretectal nucleus (APN).[216] The anterior pretectal nucleus is thought to be an important source of descending inhibition of nociceptive pathways. Evidence suggests that it sends axons to catecholaminergic neurons of the parabrachial region.[217–218]

Subnucleus Reticularis Dorsalis

The medullary SRD is active in balancing descending inhibition and facilitation of nociceptive processes. Projections from this region innervate contralateral somatosensory, motor, limbic, and insular cortex, and PAG, pons, cerebellum, trigeminal, and other brainstem nuclei.[172] Connections to the anterior cingulate gyrus participate in the descending facilitatory modulation of pain.[210] The DNIC inhibiting wide dynamic range neurons in the spinal cord competing with afferent input are dependent on a supraspinal loop through the SRD and a descending pathway.[164,174]

Descending Pathways Modulating Pain

Periaqueductal Grey

Descending inhibition of spinal nociceptive processes was initially described by Reynolds in 1969 in behavioral experiments in which electrical stimulation of the PAG resulted in antinociception.[225–227] The PAG in the midbrain makes descending connections with the rostral ventromedial medulla (RVM)[217] and the noradrenergic system of the dorsolateral pons.[218] A net inhibition of spinal nociceptive processing is initiated from the PAG through glutamate and SP inputs to these brainstem regions with major descending axonal projections. The cholinergic neuronal system that extends dendrites into the PAG is another major reticular system of the midbrain and other portions of the brainstem that

provides descending influences on nociception. The cholinergic mechanisms can reduce nociception and potentiate opiate analgesia.[219,220] These analgesic actions may be mediated through presynaptic terminations of laminae III–V cholinergic interneurons reported to synapse directly onto primary sensory endings.[221]

Raphe System

Anti-nociception because of descending modulation was proposed, based on behavioral, electrophysiologic, and morphologic studies, to occur through a PAG relay to the RVM and then to the spinal cord[222–232] (also see reviews[212,232–234]). Subsequent findings suggest that the process is mediated through more complicated brainstem circuitry (Fig. 8.9). It is now known that both inhibitory and excitatory influences on spinal cord nociceptive processing occur after activation of recurrent loops through the brainstem, activated by ascending pathways from the spinal cord. Extensive behavioral and electrophysiologic studies have found that bulbospinal facilitatory projections and, in particular, those descending from the RVM promote tactile and thermal hyperesthesias.[235–238] The RVM is responsible for the maintenance, although not the initiation, of neuropathic central[239–241] and visceral pain.[242,243] The RVM is composed of the midline raphe system and the adjacent ventral reticular formation. The raphe-spinal pathway is largely, but not entirely, serotonergic.[244–246] The component that originates from the nucleus raphe magnus (NRM) descending in the dorsolateral funiculus is primarily associated with inhibitory control, and a ventrolateral descending pathway is typically attributed with facilitatory control of nociceptive responses. Excitatory SP and inhibitory enkephalinergic connections between the NRM and the noradrenergic neurons of the dorsolateral pons are major components of the descending control system that promote both facilitatory and inhibitory influences modulating pain.[207,247] An additional supraspinal loop from the dorsal horn to the dorsal reticular nucleus and back to the dorsal horn also mediates both descending inhibition and facilitation.

Pontine Noradrenergic Neurons

Descending noradrenergic input to the spinal cord from the dorsolateral pons has been shown to limit responses to acute noxious stimulation.[211] However, elimination of the A6 locus coeruleus nucleus provides facilitation in the case of long term nociceptive activation.[248–250] The largest percentage of spinally projecting noradrenergic neurons has been identified in the locus coeruleus, subcoeruleus, and parabrachial and Kölliker-Fuse nuclei.[251–253] The noradrenergic A5 cell group in the ventrolateral pons/medulla and the adrenergic neurons of the ventrolateral medulla also send axonal projections to influence nociception in the spinal cord and thalamus.[208,253]

Anterior Pretectal Nucleus

The APN has also been associated with inhibition of nociceptive somatosensory function.[216] The anterior pretectal region evokes antinociceptive responses in the tail-flick, formalin, and paw pressure tests. However, this region has minor direct input from lamina I and X in the spinal cord, and direct innervation of the spinal cord by the APN has not been reported. Indications are that these effects are mediated through anatomic connectivity with the dorsolateral pontine pathways.

Hypothalamus

Many hypothalamic nuclei, including the LH, have descending connections to the PAG.[233,234,254] Hypothalamic axons form the largest input to the PAG.[254] The hypothalamic input to the PAG is topographic, linking particular hypothalamic nuclei with particular regions of the PAG.

Inhibition and Facilitation

While there are direct descending axons to the spinal cord, the PAG connections with the locus coeruleus and the raphe magnus are major sources of input driving descending inhibition and facilitation known to impact the perception of pain before and after the transition to chronic pain.[218–230,255,256]

Limbic Cortex

Several forebrain areas with descending projections impact nociception, including the central nucleus of the amygdala, the SI somatosensory cortex, and many parts of the limbic cortex.[178] Limbic regions include the anterior cingulate gyrus, the infra- and prelimbic cortex medially, the precentral medial cortex, and laterally the anterior and posterior insular cortex and perirhinal cortex.

The simplified schema of the supraspinal circuitry of the descending control systems imposing facilitative and inhibitory modulation of nociceptive processing is shown in Fig. 8.9. "Stress-induced analgesia" is a shift in the balance favoring descending inhibitory pathway activation. Nociceptive insults, such as nerve damage or tissue inflammation, increase the tone of both modulatory events shifting the balance toward inhibition.[230–232,255,256] While increased activation of the pain systems and increased descending inhibition predominate during pain states initially, descending inhibitory systems eventually become unable to damp the increasing nociceptive activation, ensuing in facilitation and central sensitization[250]. In truth, it is the summed effect of this complex polysynaptic inhibitory and excitatory circuitry that establishes the level of perceived pain intensity. Activation of higher brain limbic sites is evident in chronic brain states.

Centers for Higher Processing of Nociception

Perception of Pain

Early electrophysiologic studies reported parallel processing of nociceptive inputs from the thalamus to the sensory (SI, II), cingulate, and insular cortex.[178] Specific discriminative input in response to noxious somatic stimulation is received in the ventral posterolateral thalamus (VPL). The ventromedial nuclei of the thalamus receive face and tooth pulp input. This classic pain circuitry is responsible for site localization, intensity coding, and perception of pain. The midline and intralaminar thalamic centrolateral (CL) and parafascicular nuclei also receive less discriminative visceral nociceptive input when the typically silent visceroreceptors become activated by excessive stretch or inflammation.[8,9,165,180,257–259] Sensory interoception can then become a primary pain condition.[8,9,257–259]

Imaging of Pathologic Pain States

Confirmation of the activation of cortical and other brain sites became available with the advent of positron emission tomography (PET) and fMRI.[260–270] The activation indicated by an increased signal in the imaging studies on somatosensory processing regions of the ventral posterolateral thalamus, SI cortex, and SII cortex is consistent with a sensory-discriminative role of these structures.

Numerous studies have indicated that greater activation of the pain circuitry coincides with higher brain circuitry and neuroplasticity and is more easily observed in the trigeminal,

parabrachial, and amygdala circuitry.[272–275] Altered function of the brainstem pain modulation circuits, which is crucial for maintaining chronic pain, is supported by increased connectivity strength between the ventrolateral PAG and locus coeruleus with higher brain regions, including the hippocampus, nucleus accumbens, and ACC.[276]

However, improved resolution of MRI has even made it possible to confirm that pain activates many regions other than the thalamus and SI and SII somatosensory cortex observable using electrophysiology, particularly in the brains of patients with chronic pathologic pain. Imaging studies have found that the MRI signal increase indicating activation in limbic brain regions is imposed by chronic pain, and maladaptive cortical loss has also been reported.[199,200,277] In patients with pathologic pain and in persistent pain animal models, neuronal activation measured in the limbic cortex has been confirmed with imaging studies in the amygdala, medial prefrontal cortex/anterior cingulate gyrus (mPFC/ACC), and hippocampus (Fig. 8.8).[200,205,231,277,278] Altered connectivity with the amygdala, medial prefrontal cortex/anterior cingulate gyrus (mPFC/ACC), and hippocampus evident with MRI is correlated with the pain level and duration in patients with chronic pain.[198,278,279] After months of suffering, the limbic system eventually produces secondary dysfunctional affective/emotional responses symptoms, including anxiety and depression, via the mPFC/ACC and altered hippocampal cognitive function, even in research models.

Default mode circuitry activation affecting cognitive function in chronic pain patients is highlighted by increased fMRI signal intensity in the prefrontal cortex and hippocampus.[281] There is decreased coactivation in the caudate nucleus and nucleus accumbens bilaterally in multiple sclerosis patients with chronic pain.[282] The ventral striatum, including the nucleus accumbens and the caudate nucleus, is connectionally associated with the limbic structures and the prefrontal cortex and is involved in motivational and emotional aspects of behavior, including reward, which is important for planning and decision making.[284,285]

Most of the limbic regions significantly activated by pain are components of the anxiety and aversion/reward circuitry.[285,286] Intense stimulation such as noxious thermal stimuli in healthy, pain-free study participants or pathologic pain in patients activates limbic brain regions, including the ACC, prefrontal cortex, amygdala, medial dorsal thalamus, and ventral tegmental area in the base of the midbrain. The ACC and the amygdala are highly involved in the interpretation of the emotional significance of the painful input, alerting, and determining the affective response to pain.[283,285,287,288] These brain regions are responsible for affective and contextual associations of pain and pain related aversion.[285–292] Activation occurring particularly in these brain areas is involved in planning the motivational and emotional response to pain and, as such, probably reflects the maladaptive physiology of chronic pain. Optogenetic stimulation studies indicate that the excitatory projection from the parabrachial nucleus to the central nucleus of the amygdala (CeA) drives negative emotions, including anxiety, depression, and aversion, in rats.[291] In contrast, activation of excitatory projections from the basolateral amygdala to CeA counteracts each of these negative emotion behaviors. The histone deacetylase SIRT1-CaMKIIaα pathway in the central amygdala is a key epigenetic mechanism guarding against the development of comorbid emotional disorders under chronic pain, but its dysfunction causes increased vulnerability to the development of chronic pain.[293]

Chronic pain causes dysfunction of the prefrontal-hippocampal circuitry, leading to working memory deficits. The hippocampus, insula, cerebellum, ACC, and frontal cortex all contribute to memory and learning of events related to painful stimuli, such as avoidance behavior based on previous pain experience.[294,295] Chronic inflammatory pain affected the patterns of the medial prefrontal cortex-mediodorsal thalamus (mPFC-MD) activity while rats performed spatial alternation working memory.[294] In rats with spared nerve injury induced neuropathic pain, this disruption was reversed by the selective optogenetic inhibition of the prelimbic area of the mPFC CaMKIIα-expressing neurons during the last portion of the delay-period, but without any significant effect on pain responses.[293] The basal ganglia (caudate, putamen, globus pallidus) and cerebellum may have a role in the learning of reflexive motor responsiveness to painful input necessary to protect the individual.[204,296] Multiple brain networks processing sensation, affect, and cognition interact to create the pain experience and pain related decision making: for example, the nucleus accumbens is important in planning and decision.[295] Patients with subacute back pain who are at risk for becoming chronic back pain patients exhibit limbic system structural alterations, including loss of low frequency fluctuations in nucleus accumbens activity during the time that patients transition to the chronic phase, affecting its connectivity with the rostral ACC.[296]

Together with the habenula, the ACC is involved in negative outcome learning and, as such, contributes to chronic pain associated anxiety.[297–300] The habenula is considered an evaluator of numerous inputs converging on it and has connections with regions with descending input.[299] An excitatory projection from the basal ganglia to the lateral habenula (LHb) described explains how LHb-projecting basal ganglia neurons have encoding properties similar to those of LHb neurons themselves and provide a link between "anti-reward" excitatory synapses and serotonin, a neuromodulator implicated in depression.[300] Patients with ACC lesions have decreased affective responses to pain.[205] Human study participants can control experimental pain sensation by reducing the neuronal activity within the ACC.[298]

A review of these many brain regions involved in pathologic pain, their neurotransmitters, anatomic structure, and connectivity circuitry is available.[303] A more detailed discussion of the clinical correlation of these topics is available in other chapters in this volume.

Reward/Aversion Circuitry

While morphine provides relief from pain through activation of the reward circuitry, dysfunction in the parallel aversion circuitry is activated in chronic pain patients. It is well known that alterations in the reward/aversion circuitry are ongoing in the development and persistence of chronic pain and chronic pain associated anxiety and depression.[286,287] The "salience network" includes the anterior insula, amygdala, ACC, and ventral striatum and is involved in the interoception of the feelings associated with reward. The salience network is said to be functionally damaged in chronic pain patients as a consequence of a barrage of repeated painful input and positively correlated with drug craving and withdrawal.[286,287]

The posterior cingulate cortex, precuneus, medial prefrontal, and inferior parietal cortices are thought of as the "default mode network" (DMN).[300] Studies suggest that DMN activation is positively correlated with drug craving and withdrawal, while substance consumption suppresses the activity of DMN.[286,287]

The increased cross-network functional connectivity between the default mode network and the salience network is proposed as a metric of functional brain abnormality in chronic pain.[304]

Neuroplasticity and Alterations in the Pain Circuitry During Chronic Pain

The process of pain "chronification" involves stress, age, genetics, environment, and immune responsivity of individuals but is based on molecular, physiologic, neuroplastic, and even anatomic alterations,[305,306] resulting in brain remodeling that includes recruitment of limbic and aversion circuitries.[200,307–309] fMRI scans of patients with chronic back pain identified altered brain circuitry in the amygdala, medial prefrontal cortex/anterior cingulate gyrus (mPFC/ACC), and hippocampus within three to 12 months that correlated with pain level and duration.[198,199] Chronic pain can cause functional reorganization of the brain as well as reduction of gray matter volume in distinct cortical regions because of central plasticity but only at chronic time points. It can recover once the pain is alleviated.[198,310,311] Chronic pain causing concurrent activation of emotional brain circuits can produce secondary dysfunctional affective/emotional symptoms such as anxiety, depression, and altered cognitive function that alter the quality of life.[199,273,280,286–288,291,310,311] The powerful extent to which the widespread brain endogenous opioid system, with its endomorphin 1 and 2 (μ-opioid) receptors potentiated by dynorphin (δ-opioid) receptors, plays a role in these dysfunctional pain related symptoms and therapy related addiction has long been under study and is discussed in subsequent chapters.[312,313]

Conclusion

This chapter has reviewed information about the pain system circuitry from peripheral nociceptors, spinal interneurons, and projection neurons that provide the nociceptive information to higher centers. The functional and content differences of nociceptive afferents are discussed. The laminar phenotypes of excitatory and inhibitory spinal interneurons forming the basis of spinal modulation are differentiated. While primary afferent depolarization, dorsal root reflexes, gate theory, neuroglia, and neurotransmitters utilized are discussed, detailed information about how the modulation actually occurs and transitions to central sensitization is still unknown. The organization of several ascending nociceptive pathways, including the well-known lateral spinothalamic, spinomesencephalic, spinoreticular, and spinocervical tracts, is described. The lesser known medial spinolimbic, spinohypothalamic, and post-synaptic dorsal column pathways are also discussed in some detail. Description of nociceptive processing in the thalamus and cerebral cortex is left to other chapters, but brainstem regions receiving ascending nociceptive information that provide descending modulation are detailed. The analgesic/facilitatory descending systems discussed that modulate and augment the neuroplastic events leading to central sensitization include the PAG, locus coeruleus, parabrachial area, NRM, reticular formation, and APN. Several components of the limbic system are described, revealed primarily in MRI and clinical studies. With overactivation, the limbic circuitry components become dysfunctional players in the pain circuitry, often permanently altering the perception of pain. Their functions and their importance in chronic pain overshadow the basic ongoing reliable functioning of the somatosensory system. While the descriptions of the pain circuitry have been accumulating over the past four decades, the current knowledge about the basic, static physiology pales compared to the advances in our knowledge potentially available in the future. The tools available to reveal the molecular, epigenetic, and genomic events occurring in the pain systems driven under the pathologic stress of chronic pain can now be determined and will add significant knowledge at an ever-increasing pace. New findings are defining fruitful lines of research that will certainly lead to improvements in therapy for pain management.

Key Points

- Nociceptive nerve endings transduce information about internal and external mechanical, thermal, and chemical stimuli that are noxious, distressing, or damaging. Sensory nerves transmit the information centrally.
- Pain is communicated from nerve endings to the spinal cord, relayed across a synapse in the spinal cord, and then transmitted to brainstem integration sites.
- Spinal cord and spinal trigeminal dorsal horn interneurons provide state dependent signal modification, either amplifying or inhibiting the pain signal prior to the relay of information to brainstem integration sites.
- Central ascending spinothalamic pathways carry discriminative pain related information coded for location, intensity, and quality of the noxious input. Axons of lamina I spinothalamic tract neurons cross the midline and ascend in the lateral spinal cord white matter on the opposite side. Spinothalamic tract neurons in deeper laminae send their axons through the ventrolateral spinal white matter on the opposite side, through the ventrolateral brainstem, to the primary integrative site for discriminatory sensory information in the ventral posterolateral (VPL) nucleus of the thalamus.
- Discriminative information about pain is relayed by neurons of the VPL thalamus primarily to the somatosensory cortex (SI, SII) with connectivity to the motor cortex to plan and execute appropriate escape responses.
- Collateral axons of the ascending spinothalamic tract directly innervate integrative brainstem sites, including the lateral medullary and pontine reticular formation, parabrachial nuclei, PAG, hypothalamus, and amygdala. Termination sites suggest that the lateral pain related pathways impact limbic activation, emotional response, and autonomic regulation along with direct connections of the spinoparabrachial and spinoamygdalar pathways.
- Along with the spinoamygdalar and spinoparabrachial pathways, other phylogenetically older axonal pathways carry visceral pain and mechanotactile information from deep tissues arising from neurons in lamina III, VII, VIII, and X in the deep dorsal horn. These axons ascend in the dorsal column to innervate the caudal dorsal column nuclei in the midline of the caudal medulla or travel in the ventral midline and lateral white matter to innervate ventral and medial brainstem sites, pontine parabrachial nuclei, PAG, hypothalamus, amygdala,

substantia innominata, nucleus basalis of Meynardt, globus pallidus, insular cortex, and the medial and intralaminar thalamus. The termination sites of these pathways suggest they impact limbic activation, fear motivated avoidance, emotional response to pain, and autonomic responses.

- Descending input to the spinal cord modulates the primary sensory information to either facilitate or inhibit the sensory signal.
- Descending pathways to the spinal cord that modulate pain include axons originating in the PAG, raphe system, pontine locus coeruleus, and medullary reticular formation. These centers are impacted by input from higher brain centers and by incoming spinal sensory transmission.
- Complex integrative connectivity among centers for higher processing of pain, including medial and lateral thalamic, cortical, limbic, and hypothalamic sites, impact the awareness and chronification of pain, motivational responses to pain, and regulation of autonomic, emotional, and motor responses to pain. PET and MRI imaging provide better information about altered pain processing in higher brain centers and the effect of pharmacologics.

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9

Neurochemistry of Nociception

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Origins of the Pain Phenotype

For heuristic purposes, we can distinguish the three mechanistically distinct sources of a pain state: (1) high intensity stimulation, (2) local tissue injury and products released secondary to injury and inflammation, and (3) injury to the peripheral nerve. These conditions may achieve further distinction by being characterized as acute or chronic, where chronic pain is defined as persistent or recurrent pain lasting longer than three months. Exposure of the organism to these conditions will typically lead to escape from the stimulus condition, emphasizing a hallmark of pain, which is that the stimulus condition is aversive and fraught with negative re-enforcing properties. This endows a painful state with two properties: (1) it supports avoidance behavior and (2) it can provide negative connotations to otherwise innocuous stimuli with which it is paired.

Acute Nociception

In the early 1900s, Sir Charles Sherrington designated high intensity stimuli that signaled a potential injury to the body as being *nociceptive* in character. The application of such stimuli to the body produces a syndrome that includes the withdrawal of the affected body part, signs of autonomic activation, and a complex set of behavioral responses that in intact animals include agitation and vocalization. In humans, an unconditioned high intensity stimulus evokes discrete sensations that have the assigned attribute of being *painful* (e.g. the sensation initiated by picking up a very hot cup of coffee). The reported sensation refers to the site of stimulation, and the magnitude of the report or response varies with the intensity of the stimulus. Termination of the stimulus before injury results in the cessation of sensation. Accordingly, *nociception* is a descriptor that refers to the physiologic response generated by high intensity, potentially tissue-injuring stimuli, whereas *pain* represents the interpretation of that event as a sensation with highly aversive properties. Such stimuli have powerful motivating effects that can support the generation of escape behavior when cued by innocuous stimuli that have previously been paired with a nociceptive stimulus. Thus a strong shock evokes a nociceptive state from which the animal will seek to escape. A light paired with that shock will become conditionally associated with the shock, such that in a short time, the light alone can initiate the same profile of nociception.

Tissue Injury and Inflammation

Suppose the stimulus is of sufficient magnitude to result in local injury (tissue disruption, plasma extravasation). In that case, a pain sensation will persist after removal of the stimulus, and the injury will be accompanied by increased sensitivity to subsequent stimuli applied to the injury site (primary hyperalgesia) and enhanced sensitivity to stimuli applied at sites adjacent to the injury site (e.g. secondary hyperalgesia or allodynia). Again, these states of enhanced sensation indicate that the non-tissue-injuring stimulus now acquires an aversive property (e.g. warm water on a sunburn). As will be considered below, the injury yields the release of chemical products that can, through eponymous receptors, directly increase activity in afferent systems that are typically activated by high intensity, nociceptive stimuli.

As an overview, the effects of a high intensity, tissue-injuring stimulus reflect an initial activation of the primary afferents that project to the dorsal horn of the spinal cord, from which transmitters are released that activate a complex dorsal horn circuitry. Under normal circumstances, these spinal neurons respond maximally to input arising from the root projecting to the spinal segments in which the cell lies. However, even though these afferents primarily activate these homosegmental neurons, they also send collaterals rostrally and caudally up to several spinal segments away, where they make synaptic contact with neurons in adjacent segments (heterosegmental). These distal neurons are less efficiently activated than the homosegmental cells (and may not be activated sufficiently to generate an action potential). However, these homosegmental and heterosegmental cells form the real or potential dimension of the dermatome of the spinal segment. As will be shown later, if the *excitability* of these higher-order spinal heterosegmental neurons is increased, cells that were not activated by a given input become depolarized, and the size of the dermatome of a given segment will be increased. These dorsal horn neurons then project by long tracts in the ventrolateral quadrant either (1) directly to diencephalic sites (e.g. thalamus, hypothalamus) or (2) indirectly through an intermediate synapse on neurons in the medulla, pons, or mesencephalon, which then project to a variety of diencephalic and limbic forebrain sites. The anatomic details of these pathways have been discussed previously (see Chapter 8).

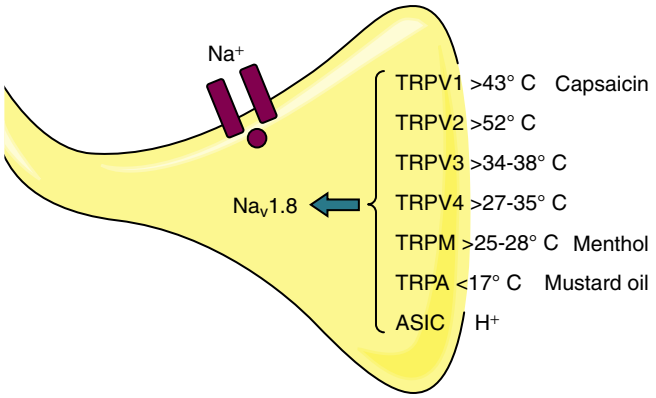
In general, the processes leading to a pain state secondary to a high intensity peripheral stimulus reflect the frequency of traffic that appears in these spinofugal pathways. Activity in the spinofugal systems is primarily dependent on the intensity of the afferent

stimulus, but as will be made evident, a variety of systems serve to increase the gain of the spinal input-output function and depress this gain. In the first case, we anticipated that there would be an increased pain sensation associated with any given stimulus, whereas in the second case, the pain sensation produced by a given stimulus would be diminished. This dynamic property of the input-output systems represents an important characteristic of systems that process nociceptive stimuli. In the following sections, we consider the transmitter pharmacology that defines these synaptic linkages.

Nerve Injury

Peripheral nerve injury may arise secondary to a variety of conditions, including physical injury (section, compression), changes in trophic functionality (ischemia, metabolic poisons), or immune interactions (as with autoantibodies). The functional phenotype of these changes is often an ongoing pain state, referring to the distribution of the injured nerve and an enhanced response to low-intensity mechanical or cold stimuli.

In the following sections, we provide an overview of the mechanisms underlying these pain states.



• **Figure 9.1** Transducer channels on a small afferent terminal. Optimal stimulus intensities for activating channels and various chemicals that also activate these channels are indicated. Different terminals express different combinations of channels, which would define the response properties of that afferent. Channel activation leads to the activation of voltage-sensitive sodium (Na_v) channels. The $Na_v1.8$ subtype of channels is frequently present only in unmyelinated axons (C-fibers).*ASIC*, Acid-sensing ion channel; *TRP*, transient receptor potential.

Primary Afferent Signaling

Acute Stimulation

The systems underlying this acute psychophysical experience begin with the primary sensory neuron, the afferent fiber. The afferents possess several intrinsic attributes.

1. In the absence of a stimulus, most primary afferents show little or no ongoing activity.
2. Activity in these afferents is initiated by various mechanical, thermal, or chemical stimuli, which activate specific populations of primary afferents.
3. The nature of the sensory information encoded by a given primary afferent is dependent on the properties of the transduction channels or receptors that are expressed on the terminals of that sensory axon.
4. The frequency of firing in these afferents generated by a particular stimulus varies monotonically with the intensity of the stimulus (e.g. temperature for a thermal-sensitive afferent). Thus the specific population of primary afferents is activated, and the frequency of discharge encode the intensity of the stimulus.
5. Sensory afferents are morphologically categorized by diameter, state of myelination, conduction velocity, and stimulus properties that lead to their activation.

Aβ axons. These are large, myelinated, fast-conducting axons and exhibit specialized transducer elements (such as the Pacinian corpuscle). These afferents are typically activated by low-intensity mechanical stimuli.

Aδ axons. These are smaller, myelinated, fast-conducting afferents with subpopulations that preferentially respond to thermal or mechanical stimuli that may be preferentially activated by low-intensity or high intensity stimuli. Those responding only to high intensity thermal or mechanical stimuli are referred to as Aϑ nociceptors. As larger myelinated axons, these Aϑ often display specialized nerve endings.

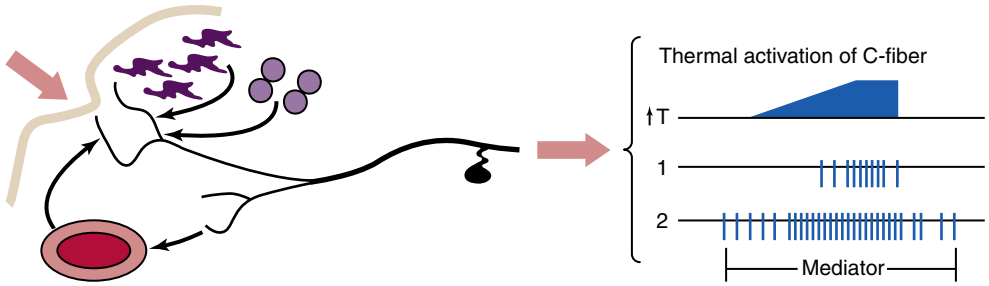
C axon. These are small, unmyelinated, very slowly conducting afferents that are activated by high intensity thermal, mechanical, or chemical stimuli. As a given C-fiber may be activated by high thermal, mechanical, and chemical stimuli, they are called *polymodal nociceptors*. In contrast to myelinated afferents, unmyelinated afferent axons typically show "free nerve endings." That is, they display no evident morphologic specialization. However, these terminals express a myriad of specific transducer channels that are sensitive to specific physical and chemical stimuli and increasingly depolarize the afferent terminal as the stimulus intensity increases. When activated by an appropriate stimulus, these channels in turn activate voltage-sensitive sodium channels that pass Na^+ and initiate action potentials. As indicated in Figure 9.1, some of these channels that transduce a physical stimulus may also be activated by various chemicals. In this case, these chemicals produce a sensation that reflects the physical stimulus that is transduced by that channel (e.g. the transient receptor potential vanilloid-1 [TRPV1] receptor is activated by capsaicin, which produces a painful burning sensation, whereas menthol activates the TRPM8 cold receptor and initiates the sensation that would be generated by low temperature).

During development, the soma of the afferent neuron starts as a bipolar neuron. However, during development, the soma buds off from the axon, remaining attached by a long sinuous glomerulus. The primary afferent axons in the periphery typically display arborization in the target tissue. Importantly, action potentials traveling from the periphery continue to the spinal dorsal horn but also travel up the glomerulus to the dorsal root ganglion cell body. Thus the dorsal root ganglion (DRG) displays depolarization. As action potential can travel down the glomerulus, the DRG can be a source of action potential generation, as can occur when an avulsed disc fragment is compressed in the DRG in the vertebral foramen.

Tissue-Injuring Stimuli

High intensity stimuli may result in local tissue injury. Such injury leads to cellular disruption, injury to local vascular integrity, and subsequent plasma extravasation, and migration of inflammatory cells such as macrophages and neutrophils. These events give rise to the release of various *active factors* from injured cells and the migration of inflammatory cells such as mast cells, macrophages, lymphocytes, and neutrophils (Box 9.1). The contents of this local milieu of an injury, often referred to as the *inflammatory soup,* acts upon eponymous receptors that are present on the terminals of many unmyelinated axons. Activation of these receptors typically

• BOX 9.1 Agents Released by Tissue Injury That Depolarize and Sensitize Small Primary Afferent Terminals



The mediators listed below are released by injury from macrophages, mast cells, and blood vessels. These mediators evoke spontaneous activity in otherwise silent C-fibers and lower the threshold for activation in response to a ramped thermal stimulus (right: one vs.).

1. **Amines.** Histamine (mast cells, basophils, and platelets) and serotonin (mast cells and platelets) are released by various stimuli, including mechanical trauma, heat, radiation, and certain products of tissue damage.
2. **Kinin.** Bradykinin is synthesized by a cascade triggered by the activation of factor XII by agents such as kallikrein and trypsin and physical trauma. It acts through specific bradykinin receptors (B1/B2).
3. **Lipidic acids.** Tissue injury activates a variety of widely distributed phospholipases that are free of AA. AA is a substrate for a large family of enzymes, such as cyclooxygenase, to synthesize lipid mediators, including prostaglandin E_2, prostacyclin, and thromboxane A_2, all of which can facilitate the excitability of C-fibers through specific membrane receptors (EP-r, IPR, and Tx-R, respectively).
4. **Cytokines.** Cytokines such as tumor necrosis factor-α and interleukin such as IL-1β are released by inflammatory cells (macrophages) and sensitize C-fibers through eponymous binding sites.
5. **Proteinases.** Thrombin or trypsin is released from inflammatory cells and activates specific receptors (proteinase-activated receptors).
6. **Neurotrophic factors.** Nerve growth factor (NGF) activates primary afferent terminals by binding to TrkA tyrosine kinase. NGF is released from fibroblasts and mast cells via injury and inflammation.
7. [H]/[K], Elevated H^+ (low pH), and high K^+ levels are found in the injured tissue. A variety of channels present on C-fibers (e.g. transient receptor potential vanilloid-1 [TRPV1]/acid-sensing ion channels [ASICs]) are activated by H^+. Acid pH potentiates terminal activation by noxious heat and other chemical mediators.
8. **Primary afferent peptides.** CGRP and substance P are found in and released from the peripheral terminals of C-fibers. These peptides produce vasodilation, plasma extravasation, and degranulation of mast cells through their respective receptors. This leads to local reddening and swelling of the skin innervated by the stimulated sensory nerve.

initiates two events: (1) an increase in intracellular calcium leading to depolarization of the terminal, leading to the discharge of the afferent, with the frequency of activation being dependent on factor concentration, and (2) activation of intra-terminal processes (phosphorylation of local membrane receptors and channels), which sensitizes the terminal such that the degree of depolarization for a given stimulus is enhanced. Such effects yield "spontaneous afferent activity," and an enhanced response to a subsequent stimulus applied to the site of injury.

The changes in the milieu of the peripheral terminal secondary to tissue damage and the accompanying extravasation of plasma occur because of increased permeability of the capillary wall (see Box 9.1). These events are responsible for the "triple response": reddening at the site of the stimulus (reflecting local arterial dilation), local edema (increased capillary permeability), and a regional reduction in the magnitude of the stimulus required to elicit a pain response (i.e. hyperalgesia).

Nerve Injury as a Stimulus

Following nerve injury arising from various insults, the organism will frequently display the development of a variety of highly aversive "spontaneous" sensations over time. This aversive component arises from aberrant ongoing afferent traffic. Sensory axons typically display little spontaneous activity in the absence of a stimulus. This is particularly true for small, high threshold afferents. However, after a chemical, immune, or mechanical injury to the nerve, afferent axons exhibit (1) an initial burst of afferent firing, (2) electrical silence for an interval of hours to days, and (3) the appearance over hours to days of "spontaneous" bursting activity in both myelinated and unmyelinated axons. This aberrant traffic may arise from several sources. This ongoing activity reflects the initial dying back of the injured axon (retrograde chromatolysis) and the initiation of sprouting. Collections of these sprouts form neuromas. Recording from the afferent axon indicates that the ongoing activity originates after an interval of days to weeks from the lesioned site (neuroma) and from the DRG of the injured nerve.

Several lines of evidence support the assertion that the ectopic activity in the afferent arising from the neuroma or the DRG of the injured axon is in part responsible for the observed pain behavior: (1) the onset of ectopic activity in the neuroma or DRG and the onset of pain behavior have parallel time courses, (2) pain behavior can be blocked by the application of tetrodotoxin (TTX) or local anesthetic to the neuroma or DRG, (3) dorsal rhizotomy transiently reverses the pain behavior, and (4) irritants applied to the DRG will initiate activity and yield pain behavior. Several changes can lead to prominent alterations in ongoing afferent activity.

Altered Channel Expression

A variety of channels in the sensory afferents can modulate excitability. Two major classes are the sodium channel, which carries the primary current for axonal depolarization, and several potassium channels. The activation of these potassium channels can reduce axon excitability. Upregulation of sodium channels or downregulation of potassium channels would have a net effect of increasing axon excitability.

Sodium Channels

A large increase in the expression of sodium channels in the neuromas and DRGs occurs after nerve injury. Several sodium channel variants exist in primary afferent neurons, including subtypes designated as $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$. Those designated as resistant to the sodium channel blocker TTX, $Na_v1.8$ and $Na_v1.9$, are found primarily in small DRG cells (C-fibers). These channels mediate slow activation and slow inactivation of sodium currents. The importance of some of these variants in nerve injury pain states is suggested by "knock-down" studies wherein reduction of, for example, $Na_v1.8$ has no effect on baseline pain thresholds but reverses nerve injury evoked pain states in animal models. In humans and animal models, systemic lidocaine at plasma concentrations that block ectopic activity can attenuate the hyperpathic state observed after nerve injury, thus confirming the importance of sodium channels in the post–nerve injury pain state. In humans, mutations in one sodium channel ($Na_v1.7$) can cause *extremely painful conditions*. Conversely, loss-of-function mutations lead to *prominent insensitivity* to pain generated by tissue-injuring stimuli. Conversely, other mutations can result in a "gain of function," which Additionally correlates with syndromes such as erythromelalgia, characterized by severe episodic pain.

Potassium Channels

Following nerve injury, potassium currents (e.g. K2P, TWIK-related K^+ channels) have been shown to be reduced, thus suggesting downregulation of these channels. Potassium channel blockers increase ectopic firing after peripheral nerve injury.

Changes in the Chemical Sensitivity of Neuromas and Dorsal Root Ganglia

Sprouted terminals of an injured axon display sensitivity to several humoral factors, including prostanoids, catecholamines, and chemokines or cytokines such as tumor necrosis factor (TNF). Several examples of how this sensitivity is related to the appearance of ongoing activities are noted.

Cytokines/Chemokines

After nerve injury, the release of various cytokines, including TNF, interleukins (IL), interferons (IFN), colony-stimulating factors, transforming growth factors, and *chemo*attractant cytokines, also called chemokines, have been noted in various local inflammatory cells. These cytokines directly activate the nerve and neuroma through eponymous receptors expressed in the membrane after nerve injury. For example, the mechanisms of TNF interactions are multiple and complicated. TNF decreases potassium conductance in neurons, whereas long-term effects may be initiated through activation of a variety of kinases (mitogen-activated protein kinases [MAPKs]). Behaviorally, the application of TNF to the nerve results in hyperalgesia, and systemic delivery of TNF-binding protein reduces free TNF and decreases pain behavior in animals with neuropathic pain.

Catecholamines

Following nerve injury, post-ganglionic *sympathetic efferents* (cell bodies in the sympathetic ganglion) and sympathetic afferents (afferents that travel with the sympathetics but the cell body for which is located in the DRG) sprouts into the peripheral injury site and the DRG of the injured axons. In response to the release of nerve growth factors from local Schwann and inflammatory cells, these post-ganglionic terminals locally release catecholamines. Physiologic studies have shown that following nerve injury, stimulation of post-ganglionic axons will excite the injured axon and the DRG of the injured axon and that such activation is blocked by α-adrenergic antagonism. After nerve injury, upregulation of sympathetic fibers and α_1-adrenergic receptors in the DRG and skin has been demonstrated. Accordingly, increased catecholamine concentrations in the vicinity of the DRG or injured neuroma can translate into enhanced activity.

Dorsal Root Ganglion

Neuronal soma, post-ganglionic sympathetic axons, satellite glial cells, macrophages, and blood vessels in the DRG are densely packed into this small niche environment. In addition to neuronal somata (small, medium, and large fibers), macrophages and satellite glial cells have been shown to play a key role in pain processing. Macrophages produce a variety of chemokines and cytokines (e.g. IL-6) that can trigger neuronal sensitization. Satellite glial cells have been shown to enhance afferent signals by increasing interneuronal communication through *gap junctions*, and satellite glial cells are involved in IL-1B and prostanoid production.

Prostaglandin Receptors

Prostanoids are released by inflammatory cells secondary to tissue injury. Activation of prostanoid receptors leads to sensitization of the primary afferent nociceptors by phosphorylation of ion channels such as TRPA1 and TRPV1. Moreover, they can enhance the opening of TTX-insensitive sodium channels by acting through eponymous receptors on the afferent terminal. TTX-insensitive channels are typically found on small unmyelinated axons, which emphasizes the association of these observations with axons carrying information having "nociceptive" content.

First-order Synapse

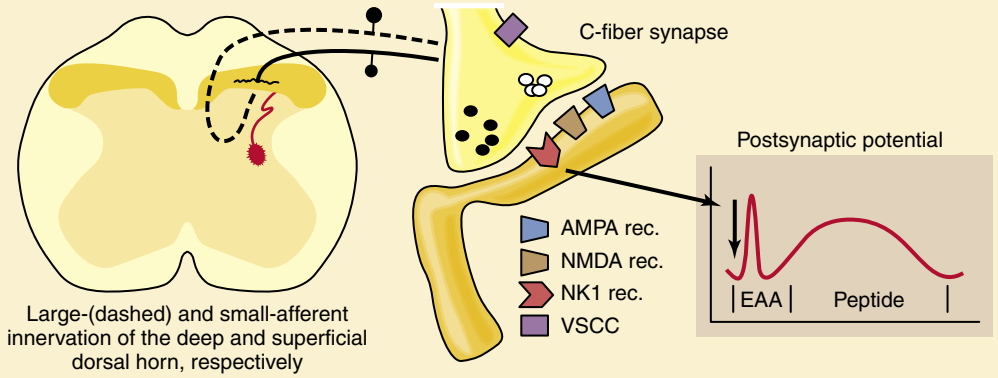
Primary afferents enter the spinal dorsal horn. Large afferents (Aβ) terminate deep to the Rexed lamina III of the dorsal horn. Aδ afferent fibers terminate superficially and in deeper laminae, whereas C-fibers generally terminate superficially in laminae I and II (marginal layer and substantia gelatinosa).

Primary Afferent Transmitters

It has classically been appreciated that primary afferent input results in a postsynaptic excitatory event, thus emphasizing that primary afferent transmitters are uniformly excitatory. In general, it appears that the principal primary afferent neurotransmitter evoking acute excitation is glutamate. It is present in the synaptic vesicles of most spinal afferent terminals, and its synthetic enzymes have been identified in virtually every primary afferent DRG cell body, regardless of the size or state of myelination. These acute effects are mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-type glutamate ionophores present on second-order neurons. This receptor produces a robust but short-lasting depolarization of the postsynaptic membrane by increasing sodium conductance (Table 9.1).

In addition to glutamate, populations of primary afferents may contain and release several neuropeptides, notably substance P (SP) and calcitonin gene-related peptide (CGRP), as well as certain growth factors such as brain-derived neurotrophic

TABLE 9.1 Summary of Primary Afferent Transmitter Organization



Primary Afferent Transmitter	Receptor	Postsynaptic Action
	Peptides	
Substance P **CGRP**	**Neurokinin 1 (NK1)** **CGRP1**	**G Protein Coupled; Slow, Long-lasting Depolarization**
Prostaglandin	EP1-EP4	
	Purine	
Adenosine triphosphate	P2X-r (P2X1-P2X7) P2Y1-P2Y14	Ligand-gated ion channels that differ in ion selectivity and gating properties Metabotropic G protein coupled receptors
	Excitatory Amino Acid	
Aspartate, glutamate	AMPA-r	Sodium ionophore; rapid short-lasting depolarization; gates sodium A subtype of the AMPA receptor can also gate calcium
	NMDA-r	Calcium ionophore; slow onset, long-lasting; gates calcium

AMPA, DL-α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; *CGRP*, calcitonin gene-related peptide; *EAA*, excitatory amino acid; *NK1*, neurokinin 1; *NMDA*, *N*-methyl-D-aspartate; *rec.*, receptor; *VSCC*, voltage-sensitive calcium channel.

factor (BDNF). Given the complexity of coding, it is likely that a variety of transmitters processes nociceptive information. The transmitters in these small high threshold afferents display several general properties.

1. Consistent with their location in small afferent terminals, high levels of peptides are present in laminae I and II, and these levels are reduced by rhizotomy or ganglionectomy or by treatment with the small afferent neurotoxin capsaicin. The sensitivity of these afferents to capsaicin indicates that one important characteristic of many (but not all C-fibers) is the expression of the TRPV1 (capsaicin) receptor. A second population of C-fibers that do not express TRPV1 typically expresses a second marker (isolectin B4 [IB4]). These IB4-positive afferents characteristically project to the deeper layers of the dorsal horn and do not express neuropeptides.
2. Glutamate and many peptides are co-contained and co-released (e.g. glutamate, SP, and CGRP in the same C-fiber terminal).
3. Release is dependent on the opening of voltage-sensitive calcium channels, and the magnitude of release is proportional to the stimulus frequency.
4. Iontophoretic application of glutamate and the peptides found in primary afferents onto the dorsal horn will produce postsynaptic excitation. Amino acids produce a rapid, short-lasting depolarization, whereas peptides produce a delayed and long-lasting discharge (see Table 9.1).

Regulation of Dorsal Horn Excitability

As noted in the introduction, the intensity of the painful stimulus is encoded in the projection to higher centers by the frequency of the output function. Accordingly, factors that enhance the excitability of spinal afferent terminals (leading to increased release of the transmitter) or the excitability of the dorsal horn projection neuron will increase the apparent magnitude of a given stimulus. In contrast, factors that diminish the excitability of the primary afferent or the projection neuron will lead to a reduction in the apparent stimulus intensity. In the following section, we will consider substrates that enhance and diminish the response of the dorsal horn to a given stimulus.

Facilitation of Dorsal Horn Excitability

Persistent small (C-fiber), but not large (A-fiber) afferent activation of lamina I (marginal cell) and lamina V (wide dynamic range [WDR]), as occurs with tissue injury and inflammation, has been shown to (1) enhance the response to subsequent dorsal horn input and (2) increase the receptive field of the activated neurons. Thus, the conditioning afferent input increases the receptive field

size of the neurons such that afferent input from dermatomal areas that previously did not activate the given neuron evokes a prominent response. Moreover, low threshold tactile stimulation has also become increasingly effective in driving these neurons. This phenomenon, first described by Lorne Mendell and Patrick Wall in the mid-1960s, is broadly referred to as "wind-up" These physiologic effects reflect events that are referred to as *central* or, more specifically, *spinal sensitization* and are believed to underlie the psychophysical correlates of tissue injury, wherein tissue injury leads to hyperalgesia and secondary hyperpathia (e.g. increased sensitivity to stimuli applied outside the area of injury). The relevance of this small afferent evoked facilitation in humans has been emphasized in psychophysical studies in humans. Here, local activation of C-fibers by the intradermal injection of capsaicin leads to an initial pain report followed by a surrounding region that shows enhanced mechanical and thermal sensitivity for an extended period. This effect is blocked by a transient local anesthetic block of the nerves innervating the capsaicin-injected area. These observations emphasize that ongoing small afferent inputs can initiate the central sensitization of pain processing.

Based on the above commentary, a decrease in C-fiber evoked excitation in the dorsal horn produced by a reduction in the release of a small afferent transmitter or block of the postsynaptic receptor (e.g. AMPA for glutamate) will diminish the magnitude of the afferent drive and, accordingly, diminish the facilitated processing evoked by protracted small afferent input. However, the facilitated state reflects more than the repetitive activation of a simple excitatory system.

Glutamate Receptors and Spinal Facilitation

The first real demonstration of the unique pharmacology of the facilitated state was achieved by showing that spinal wind-up was prevented by the spinal delivery of antagonists of the *N*-methyl-D-aspartate (NMDA) receptor, a glutamate ionophore composed of several subunits that are potently excitatory. When activated, it passes a large amount of Ca^{2+} and Na^{+} currents. It is important to note that NMDA antagonists do not affect acute evoked activity but reduce the wind-up induced by repetitive C-fiber stimulation. Correspondingly, behavioral studies have revealed that such drugs have no effect on behavior evoked by acute noxious stimuli (e.g. acute thermal escape) but do reduce the hyperalgesia observed after tissue injury and inflammation.

The absence of an effect of NMDA antagonism on acute afferent evoked activation, or the pain state reflects an important property of this receptor. At the resting membrane potential, the NMDA receptor displays a blocking of the channel by Mg^{2+}. Occupancy of the NMDA receptor by glutamate does not activate ionophores in the presence of Mg^{2+}. With ongoing depolarization of the membrane (as produced during repetitive stimulation) secondary to the activation of AMPA and SP receptors, the Mg^{2+} block is removed. If several allosteric binding sites on the NMDA ionophore are occupied (glycine/polyamine sites), glutamate may activate the NMDA channel and permit the passage of Ca^{2+} and Na^{+} currents. This opening thus serves to further depolarize the membrane and, importantly, increase intracellular Ca2+, which initiates downstream components of the excitatory and facilitatory cascade (see below).

It has become increasingly apparent that although AMPA mediates acute depolarization, reflecting an increase in Na^{+} influx in the presence of repetitive stimulation, Ca^{2+} permeability develops in the AMPA channels (e.g. calcium-permeable AMPA channels with a distinct antagonist pharmacology). Importantly, nerve injury increases the prevalence of calcium-permeable AMPA channels in spinal dorsal horn neurons.

Downstream Cascades

Primary afferent C-fibers release peptides (e.g. SP and CGRP), purines (adenosine triphosphate [ATP]), and excitatory amino acid (glutamate) products. These peptides and excitatory amino acids induce excitation in the second-order neurons. As noted for glutamate, direct monosynaptic excitation is mediated by AMPA receptors (i.e. acute primary afferent excitation of WDR neurons is not mediated by NMDA or neurokinin 1 [NK1] receptors). This initial activation leads to the enablement of the NMDA ionophore (and the generation of Ca^{2+}-permeable AMPA channels), which in turn initiates several complex cascades that reflect processes that serve to "sensitize" the postsynaptic dorsal horn neurons. Several primary examples of such facilitatory cascades initiated by repetitive small afferent inputs are presented below.

Local Neuronal Circuits

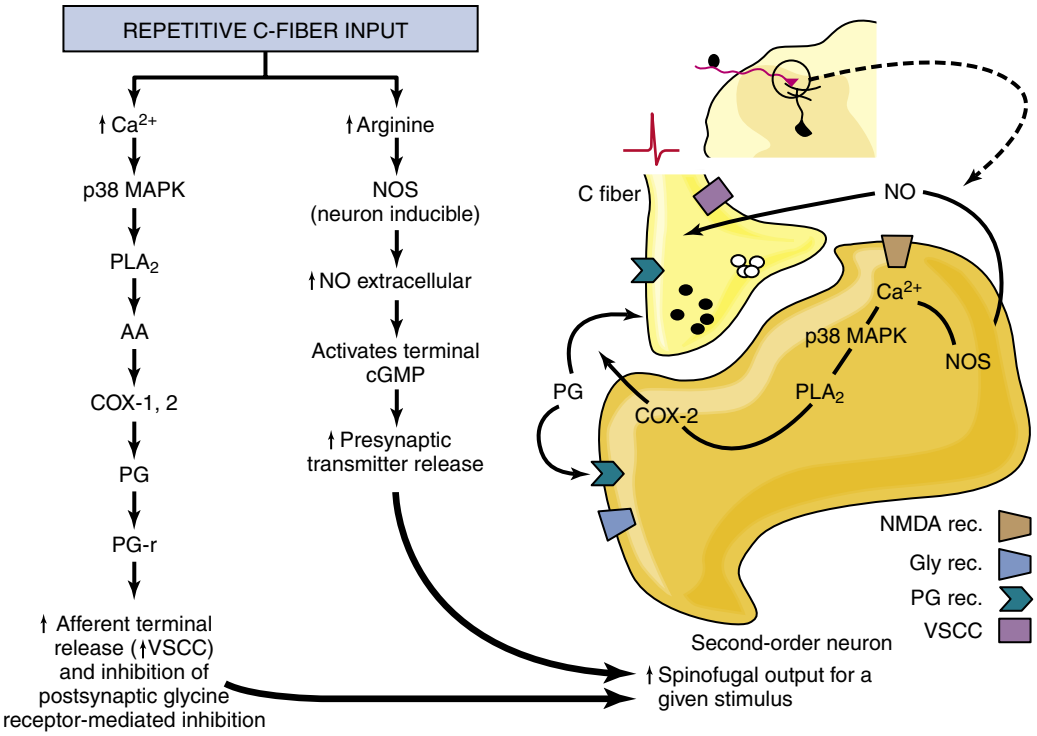
NMDA Receptors. The best example of a cascade initiated by a small afferent input is the activation of the NMDA receptor. As noted above, with ongoing membrane depolarization, the NMDA ionophore loses its Mg^{2+} block, which allows a large increase in intracellular Ca^{2+}.

AMPA Receptors. Although the AMPA receptor is largely considered an acutely activated ionophore that allows the primary passage of sodium, structural variants on the AMPA receptor allow it to pass calcium. This Ca^{2+} permeability is determined by the absence of a specific AMPA receptor subunit, GluA2. GluA2-lacking AMPA receptors are believed to participate along with the NMDA receptor in various aspects of spinal facilitation.

Neurokinin 1 Receptors. NK1 receptors are G protein coupled receptors that are activated by SP released from small primary afferents. Activation of this receptor leads to prolonged depolarization and mobilization of intracellular calcium. Spinal delivery of agents that block the NK1 site for SP can diminish the wind-up and significantly reduce the second-phase response to intradermal formalin injection.

Prostaglandin Cascade. The increase in intracellular calcium promotes the transmigration of various phospholipases to the membrane, where they then serve to cleave arachidonic acid. Arachidonic acid serves as a substrate for cyclooxygenase (COX) to produce several prostanoids. All these enzymes have been found to be constitutively expressed in spinal neurons and non-neuronal cells. This cascade leads to the release of several prostaglandins that act on a number of eponymous receptors that are presynaptically located on the primary afferent terminal and *postsynaptically* on second-order neurons. The presynaptic effect has been shown to enhance the opening of voltage-sensitive calcium channels, which mediate vesicular mobilization and release of the transmitter. A postsynaptic action that attenuates the activation of *inhibitory* glycine receptors has been demonstrated. This leads to a loss of regulatory inhibition that otherwise limits postsynaptic activation. This results in an enhanced response of the second-order (projection) neuron to a given afferent input (Fig. 9.2).

Nitric Oxide Synthase. Small afferent inputs also lead to the activation of nitric oxide synthase (NOS). Neuronal NOS and inducible NOS are both present in neurons and other cells. In the presence of arginine, nitric oxide forms and diffuses to act presynaptically (retrograde transmission) through cyclic guanosine monophosphate to enhance the release of transmitters



• **Figure 9.2** Small afferent input activates second-order neurons, leading to increased intracellular calcium, which initiates several intracellular cascades. (1) Activation of phospholipase A_2 (PLA_2) increases free arachidonic acid (AA). This serves as a substrate for cyclooxygenase (COX-1 and COX-2), which leads to the release of a number of prostaglandins (PG) that act on a variety of eponymous prostanoid receptors that are located presynaptically on the primary afferent terminal and postsynaptically on the higher-order neurons. See text for further comment. (2) Activation of nitric oxide synthase (NOS) in the presence of arginine leads to the release of nitric oxide (NO), which diffuses to enhance the release of a transmitter (e.g. glutamate). These events can serve to increase terminal release and increase postsynaptic excitability. *cGMP*, Cyclic guanine monophosphate; *Gly*, glycine; *NMDA*, *N*-methyl-D-aspartate; *p38 MAPK*, p38 mitogen-activated protein kinase; *rec.*, receptor; *VSCC*, voltage-sensitive calcium channel.

(e.g. glutamate). These events can serve to increase the terminal release and postsynaptic excitation (Fig. 9.2).

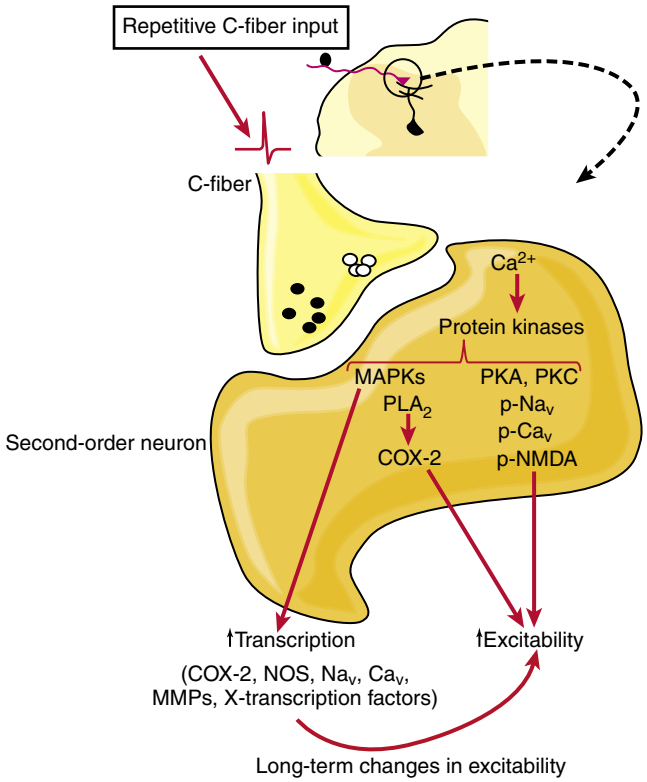
Phosphorylation. As noted, small afferent input serves to increase intracellular Ca^{2+} in second-order neurons. This leads to the activation of several protein kinases, such as protein kinase C (PKC), protein kinase A, and mitogen-activated protein kinase (MAPK) (Fig. 9.3). There are many isoforms of these kinases. All serve to phosphorylate consensus sites on various proteins. PKC has been shown to phosphorylate amino acid sites on the NMDA and AMPA receptors. This phosphorylation tends to lower the threshold for activation, which leads to greater membrane permeability. The NMDA ionophore serves to lower the threshold for removal of the Mg^{2+} block, which otherwise prevents channel activation. p38 MAPK, when activated, phosphorylates phospholipase A_2, thereby leading to its activation (see Fig. 9.2), which activates various transcription factors, such as the nuclear factor NF-κB, which serves to increase the synthesis of various proteins, such as COX, and a variety of channels (Na_v, Ca_v), receptors (TRPV1), and transcription factors (activation transcription factor 3 [ATF-3]).

Bulbospinal Pathways. Of particular interest is the growing appreciation that small afferent inputs can initiate facilitated activation through spinobulbospinal linkages (Fig. 9.4). Thus it has been shown that C-fibers make synaptic contact with superficial dorsal horn neurons (lamina I neurons). These neurons project into the brainstem and make synaptic contact with the medullary midline raphe spinal neurons that are serotonergic. These cells, in turn, project into the spinal dorsal horn and make synaptic contact with several neuronal populations but, importantly, those with cell bodies in the deep dorsal horn (lamina V). The serotonergic projections act through excitatory 5-HT_3 receptors to enhance the firing of these lamina V neurons. As stated, these cells are noted for their ability to display a facilitated state called "wind-up." Blocks of this bulbospinal linkage or the use of 5-HT_3 inhibitors have been reported to reduce this facilitated state.

Non-neuronal Cells

The central nervous system contains a wide variety of non-neuronal cells. Astrocytes and microglia are among these proteins. These astrocytes, microglia, and neurons form a complex network in which each can influence the excitability of others (Fig. 9.5).

Transmitter Mediators of Non-neuronal Cell Activation. Primary afferents and intrinsic neuron transmitters (glutamate, ATP, and SP) can overflow from the synaptic cleft to these adjacent non-neuronal cells, leading to their activation. Activation of neurons can result in the release of chemokines such as fractalkine. Astrocytes may communicate with microglia by releasing several products, including glutamate/cytokines and "S-100" protein. These products have eponymous receptors, which can lead to changes in the biology of astrocytes and microglia, resulting in the extracellular movement of a variety of neuroactive products, such as free radicals, cytokines (such as interleukin-1β [IL-1β] and TNF), BDNF, and a host of lipid mediators, including arachidonic acid, platelet-activating factor, prostaglandins, and leukotrienes. Notably, many glial cytokines, chemokines, and growth factors can modulate synaptic activity at nM concentrations,



• **Figure 9.3** Small afferent input serves to increase intracellular calcium in second-order neurons, which activates several protein kinases such as PKC and PKA or MAPKs, which serve to phosphorylate various proteins. Specifically, in this schema, PKC and the NMDA and AMPA receptors are phosphorylated, which leads to lower activation thresholds. When activated, p38 MAPK phosphorylates PLA_2, which results in its activation (Fig. 9.2) and serves to activate various transcription factors (e.g. nuclear factor κB) that increase the synthesis of various proteins (e.g. COX) and a variety of channels (Na_v, Ca_v), receptors (transient receptor potential vanilloid 1 [TRPV1]), and transcription factors (activation transcription factor 3 [ATF-3]). *AMPA*, DL-α-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid; *COX*, cyclooxygenase; *MMP*, matrix metalloproteinase; *NMDA*, *N*-methyl-D-aspartate; *NOS*, nitric oxide synthase; *PLA_2*, phospholipase A_2; *rec.*, receptor; *VSCC*, voltage-sensitive calcium channel.

while μM concentrations of neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), and glycine are necessary to produce synaptic effects. Astrocytes have the well-known ability to regulate extracellular glutamate through an active uptake system. Conversely, these intracellular glutamate stores can be released during certain activation or stress, resulting in significant increases in extracellular glutamate concentration.

Gap Junctions. Astrocytes may communicate over a distance by the spread of excitation through local non-synaptic contacts, referred to as "gap" junctions. These junctions represent specialized proteins (hexagonal multimers made up of connexin macromolecules) that serve to link the adjacent membranes of two cells. Through such linkages, local excitation in one astrocyte can lead to increased Ca^{2+} reversal of a glutamate transporter and increased extracellular ATP, which can depolarize local neuronal processes and produce local cerebrovascular constriction. Although classically limited to astrocytes, it is currently evident that such linkages may also occur between astrocytes, neurons, and microglia. Thus the gap junction represents a mechanism whereby a syncytium of excitability can be created.

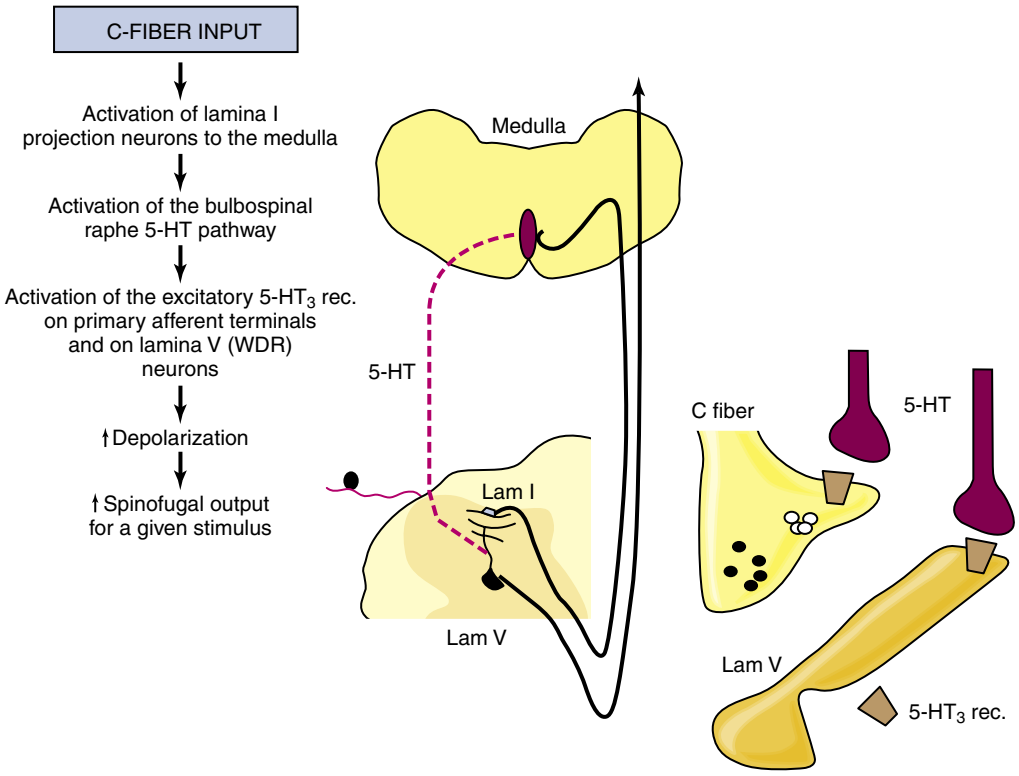
Circulating Factors. Finally, circulating cytokines (such as IL-1β and TNF) can activate perivascular astrocytes and microglia after tissue injury and inflammation. As noted, microglia are, in fact, brain-resident macrophages. Such mechanisms provide an important linkage for the somatic sensations associated with systemic infection (e.g. in the course of a common cold or the "flu").

The relevance of the non-neuronal cell population to the facilitation process in pain processing after peripheral injury is supported by a variety of observations. First, peripheral injury and inflammation lead to acute and chronic activation of microglia and astrocytes. Thus p38 MAPK-β is present in microglia and is activated in minutes after a peripheral injuring stimulus. Over longer periods, other markers of microglia (OX42) and astrocytes (glial fibrillary acidic protein [GFAP]) showed a significant increase in expression. Drugs such as minocycline (a second-generation tetracycline) and pentoxifylline have been reported to block microglial activation and diminish hyperalgesic states. Similar metabolic inhibitors that block astrocyte activation (fluorocitrate) can also diminish hyperalgesia after nerve and tissue injury. These agents, though not clinically implemented, suggest important directions for drug therapy development.

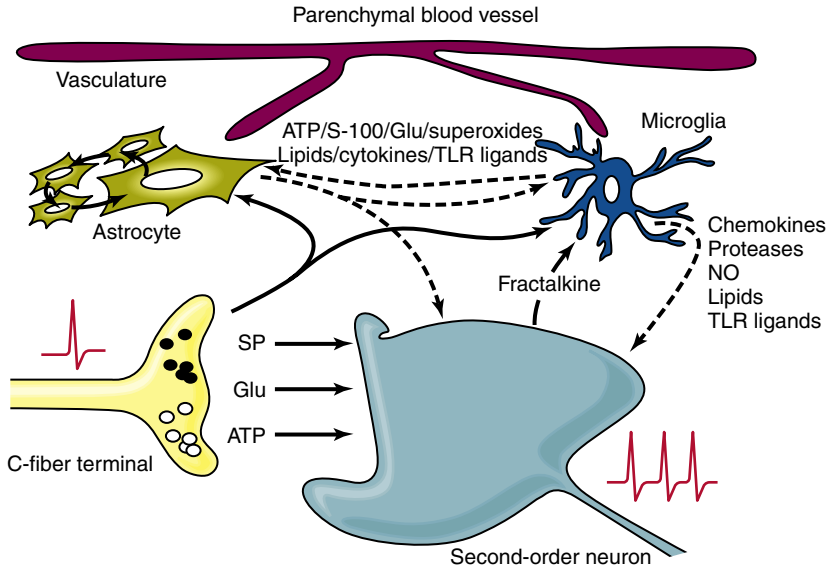
Innate Immune Systems. It has become increasingly appreciated that components of the innate immune response system may also play a role in the development of ongoing pain after an injury. One component is toll-like receptors (TLRs). TLRs recognize molecules derived from damage and infectious products and are expressed in cells involved in immune function (e.g. macrophages and neutrophils). They are also found in the spinal cord neurons, glial cells, and DRGs. Several TLRs have been implicated in pain processing through the use of mutant mice. These receptors signal via a complex series of downstream cascades that can lead to signaling mediated by a wide variety of cytokines. For example, in DRG neurons, consistent with the expression of TLR messages, TLR4 agonists increase intracellular calcium levels, thereby leading to the release of neurotransmitters. It is important to note that many ligands, such as tenascin C, which can activate various TLRs, are generated in neuraxial tissue after peripheral injury and inflammation.

Adaptive Immunity

It is appreciated that in the face of tissue injury and inflammation, autoantibodies are formed that enter the circulation. These antibodies can have two types of interactions. Some may recognize specific epitopes, such as membrane-expressed proteins, such as for a potassium channel. Binding to this channel may lead to its disablement. In this case, the loss of a potassium channel function would lead to increased excitability of the membrane. Similarly, the antibody may recognize an inhibitory receptor such as glycine, which would lead to a loss of inhibition and increased excitability. In addition, autoantibodies can form immune complexes and may interact with traditional adaptive immune signaling receptors, such as Fcgamma receptors expressed on inflammatory cells as well as afferent neurons. In this case, the binding might lead to activation of the membrane through Fcgamma signaling to the generation of a complement reaction leading to the activation of inflammatory cells. Importantly, it has been shown that antibodies from certain states, such as fibromyalgia, may express autoantibodies, which lead to a hyperpathic state when injected into a normal mouse. Such autoantibodies have also been identified in nerve injury (see below).



• **Figure 9.4** Small afferent evoked activation of lamina I neurons that project into the medullary raphe nuclei and serve to excite bulbospinal serotonin (5-hydroxytryptamine [5-HT]) pathways that activate excitatory 5-HT_3 receptors on lamina V neurons. This projection serves to facilitate the firing of these lamina V projection neurons and may underlie the phenomenon of "wind-up." *rec.*, receptor; *WDR*, wide dynamic range.



• **Figure 9.5** Schematic showing the complex assemblage in the dorsal horn with respect to astrocytes, microglia, and neurons. Products released from neurons can activate the release of a variety of active products from astrocytes and microglia. Astrocytes can activate other astrocytes through gap junctions, activate microglia, and induce the excitability of neurons by releasing a variety of active factors. As indicated, postsynaptic neuronal activation can lead to the release of chemokines such as fractalkine, which can act on eponymous receptors on microglia. See text for further details. *ATP*, Adenosine triphosphate; *Glu*, glutamate; *NO*, nitric oxide; *SP*, substance P; *TLR*, toll-like receptor.

Spinal Facilitatory Systems

The preceding section reviewed several systems that serve to increase the gain of the spinal transmission system. This facilitation serves two interrelated functions. First, it explains in part the mechanisms whereby a peripheral injury that leads to repetitive small afferent input can result in a potent hyperalgesic state (i.e. the response to any subsequent afferent stimulus is enhanced). Second, following local injury, there is frequently the development of enlarged receptive fields that extend beyond the territory of the original injury. As discussed earlier, the dermatome for any given root is represented in part by spinal collaterals of afferents that project to neurons in adjacent segments. When these cells undergo facilitation, the input from distal dermatomes becomes sufficient to drive activity in these cells. Accordingly, the receptive field of that cell now incorporates this distal body surface. Given this perspective, it is not surprising that agents targeted at these facilitatory mechanisms can profoundly affect injury-induced pain states. Agents such as COX inhibitors are an important example for emphasizing the role of the facilitated state in the pain experience. COX inhibitors diminish hyperesthesia secondary to tissue injury. This reaction reflects the important role of prostaglandins released in the periphery and in the spinal cord, where they can facilitate the release of C-fiber transmitters such as

SP. Current evidence suggests that both COX-1 and COX-2 are important constitutive enzymes in the spinal system. However, spinal COX-2 inhibitors appear to be particularly important in regulating injury-induced spinal facilitation. Nonetheless, work also points to other facilitatory mechanisms that may likewise be useful targets in the development of future agents. The potency of NOS inhibitors on behavior suggests the importance of the spinal release of nitric oxide in facilitatory processes leading to hyperalgesia. Agents that inhibit microglial and astrocyte activation can also diminish hyperalgesia. Though not clinically useful or defined as safe after spinal delivery, these agents suggest important directions for drug therapy development.

As a final *caveat* to this discussion of neuraxial facilitation, it is important to note that central facilitation studies examining the effects of repetitive C-fiber stimulation on dorsal horn neurons (described earlier) are conducted in animals that are under minimum alveolar concentration anesthesia (1 MAC, typically isoflurane or halothane). Indeed, behavioral models of facilitation wherein the injury are induced under the effect of a systemic anesthetic (e.g. barbiturate, volatile agent) show that the hyperalgesic state may be initiated although the injury is produced under anesthesia. The relevance of this observation to the performance of surgery on patients "anesthetized" with volatile anesthetics or with barbiturates alone is clear. Though preventing the ascending pain message, these anesthetics surprisingly do not appear to block the facilitatory processes that are initiated by small afferent input, probably at the level of transmitter release at the first spinal synapse. This lack of anesthetic effect on primary afferent release is believed to represent the basis of the consideration for the concept of "preemptive analgesics" via such therapeutic approaches as regional anesthesia.

Spinal Inhibitory Systems

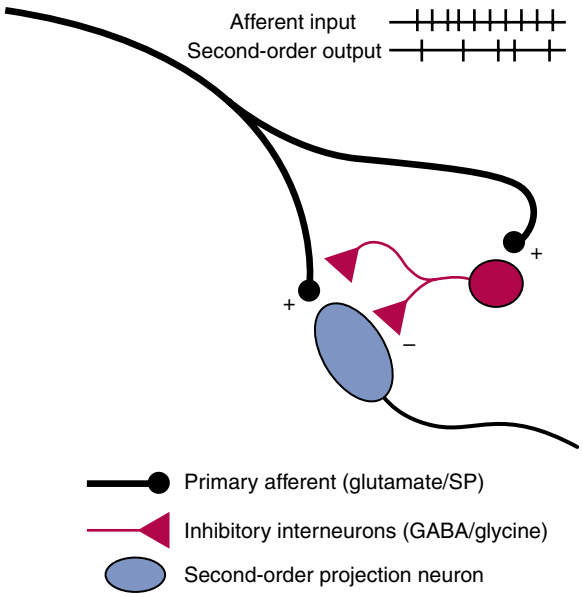
Second-order dorsal horn neurons (WDR neurons) receive excitatory input from large afferents, as well as from excitatory interneurons. This input is typically mediated by glutamate. The output from the spinal dorsal horn evoked by such excitation is subject to upregulation of excitability, but it has long been appreciated that these cells are also subject to mechanisms that downregulate local excitability. In the following sections, we will consider the pharmacology of these processes.

Local Inhibitory Circuits

This section considers systems that are local to the dorsal horn and regulate the local excitability.

Inhibitory Amino Acids

Based on the effects of various inhibitory amino acid antagonists, it appears that the excitatory effect of primary afferents, both small and large but particularly large (Aβ) ones, are subject to potent inhibition that is expressed by inhibitory γ-aminobutyric acid (GABA) and glycine receptors, which are both presynaptic on the primary afferent and postsynaptic on the second-order neuron. This relationship is shown in Figure 9.6. The release of GABA and glycine from local interneurons act on $GABA_A$/$GABA_B$ receptors and glycine receptors, respectively. The $GABA_A$ receptor and glycine receptors are ionophores that, when activated, serve to increase Cl– conductance. Based on resting transmembrane Cl– gradients, such an increase in permeability leads to modest membrane hyperpolarization and an increase in the shunting current.



• **Figure 9.6** Schematic showing presynaptic and postsynaptic regulation by glycine/γ-aminobutyric acid (GABA) interneurons of Aβ afferents input onto a second-order dorsal horn neuron. As indicated, the afferent input activated the second-order projection neurons and inhibitory interneurons. The delay in GABA/glycine release results in delayed inhibition of the second-order neurons. This results in a sculpting of second-order neuron output. In the absence of such inhibition, the afferent input yields a pronounced increase in second-order neuron outflow: *SP*, substance P.

These effects reduce the ability of excitatory input to depolarize cells. $GABA_B$ receptors are G protein coupled receptors that are also inhibitory. The relevance of this ongoing inhibitory organization to ongoing sensation is substantiated by the fact that local application of $GABA_A$ (bicuculline) or glycine (strychnine) receptor inhibitors will lead to powerful augmentation of the discharge of dorsal horn neurons evoked by large (Aβ)-afferent input.

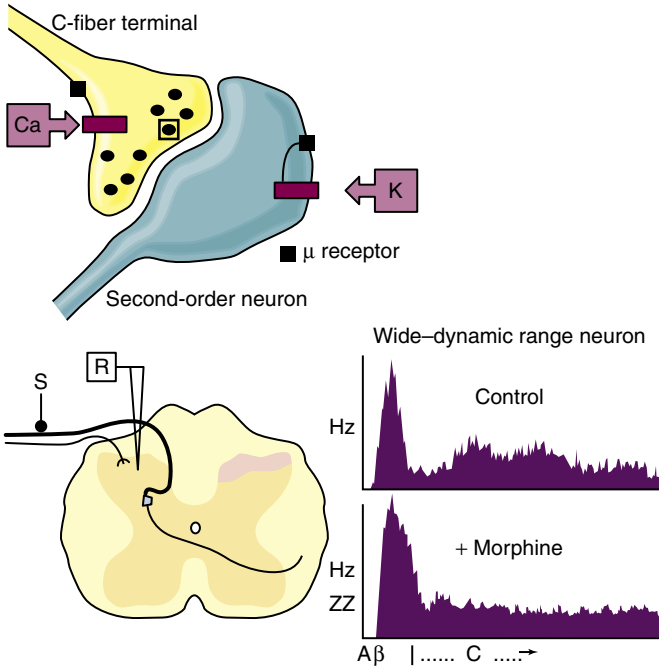
Opioids

The potent analgesic effect of opiates reveals the efficient role played by opiate receptors in regulating pain transmission. A systematic study has shown that opiate receptors that regulate the pain response are located at the spinal level and in several brain loci.

Spinal Opiate Action

Intrathecal delivery of opiate agonists will potently inhibit the injury evoked discharge of superficial and deep dorsal horn neurons induced by small high threshold afferents (C-fiber). The deep dorsal horn neurons also receive input from low threshold large (Aβ) afferents, but this evoked component is not typically blocked by opiates. These effects are mediated by an action on opioid receptors (typically characterized as μ-opioid based on agonist and antagonist pharmacology). Localization of these μ receptors has revealed that they are largely on C-fiber primary afferents that terminate in the superficial dorsal horn and on the dendrites and cell bodies of deeper dorsal horn neurons (Fig. 9.7).

Intrathecal administration will reliably attenuate the response of the animal to a variety of unconditioned somatic and visceral stimuli that would otherwise evoke organized escape behavior in all species. Confirmation of the presynaptic action is provided by the observation that opiates reduce the release of primary afferent



• **Figure 9.7** Opiate receptors are located presynaptically and postsynaptically on small primary afferents terminating in the substantia gelatinosa. A local action of opiates in the spinal cord will selectively depress the discharge of spinal dorsal horn neurons activated by small (high threshold, delayed) but not large (low threshold, short latency) afferents. C, C-fiber; R, recording electrode; S, stimulating electrode.

peptide transmitters, such as the SP contained in small afferents. The presynaptic action corresponds to the ability of opiates to prevent the opening of voltage-sensitive Ca^{2+} channels, thereby preventing mobilization and release of the transmitter. Postsynaptic action is demonstrated by the ability of opiates to block the excitation of dorsal horn neurons evoked by glutamate, a process reflecting direct activation of the dorsal horn. The activation of potassium channels leading to membrane hyperpolarization is consistent with direct postsynaptic inhibition.

Supraspinal Opiate Action

Direct injection of opiates into the brain has shown that opioid receptors that modulate pain behavior are found in several restricted brain regions, including the amygdala and the midline medulla. However, the best characterized supraspinal sites identified in this study are the mesencephalic periaqueductal gray (PAG). Microinjection of opiates into this region blocks the nociceptive response in a naloxone-reversible fashion. Several mechanisms exist whereby opiates acting in the PAG may alter nociceptive transmission.

1. Activation of bulbospinal projection. In the PAG, opiate receptors are presynaptic on GABAergic terminals that inhibit projection to the medulla. Morphine acts to block the release of GABA, which terminates inhibitory control over PAG outflow. The PAG has excitatory projections into the medulla, which then activates the bulbospinal noradrenergic and serotonergic pathways. Noradrenergic projections act through spinal α_2-receptors to reduce dorsal horn excitation.
2. Opiate binding within PAG. Such binding may be preterminal to the ascending spinofugal projection. This preterminal action inhibits input into the medullary and mesencephalic cores.
3. Outflow from the PAG. PAG outflow can increase the excitability of the dorsal raphe and locus coeruleus/lateral tegmental nuclei from which ascending serotonergic and noradrenergic projections, respectively, originate and project to the limbic forebrain. These projections were thought to modulate emotionality (see later).

These three mechanisms are summarized in Figure 9.8.

Endogenous Opiates

Opiate receptors are presumed to be targeted by endogenous compounds released from local interneurons. Several such functionally qualified families of agents have been identified according to the family of prohormones from which they are derived: proenkephalin (enkephalins), prodynorphins (dynorphins), and pro-opiomelanocortins (β-endorphin). Other endogenous opioids, such as endomorphins, have also been described. These peptides have been shown to have a significant affinity for one or more of the several identified opioid receptors. Enkephalins have been found in the dorsal horn interneurons and bulbospinal pathways. Such interneuronal systems are present throughout the brain. β-Endorphin is present in long projection pathways that largely originate in the hypothalamus. Although opiate receptors can regulate spinal nociceptive processing, surprisingly limited data suggest that endogenous systems have a robust effect on pain processing. Naloxone, an opioid antagonist, has a modest effect on ongoing pain processing. Enkephalins are rapidly metabolized by various peptidases, and changes in the pain threshold in animal models have been shown to alter pain thresholds in several experimental pain states.

Bulbospinal Projection Systems

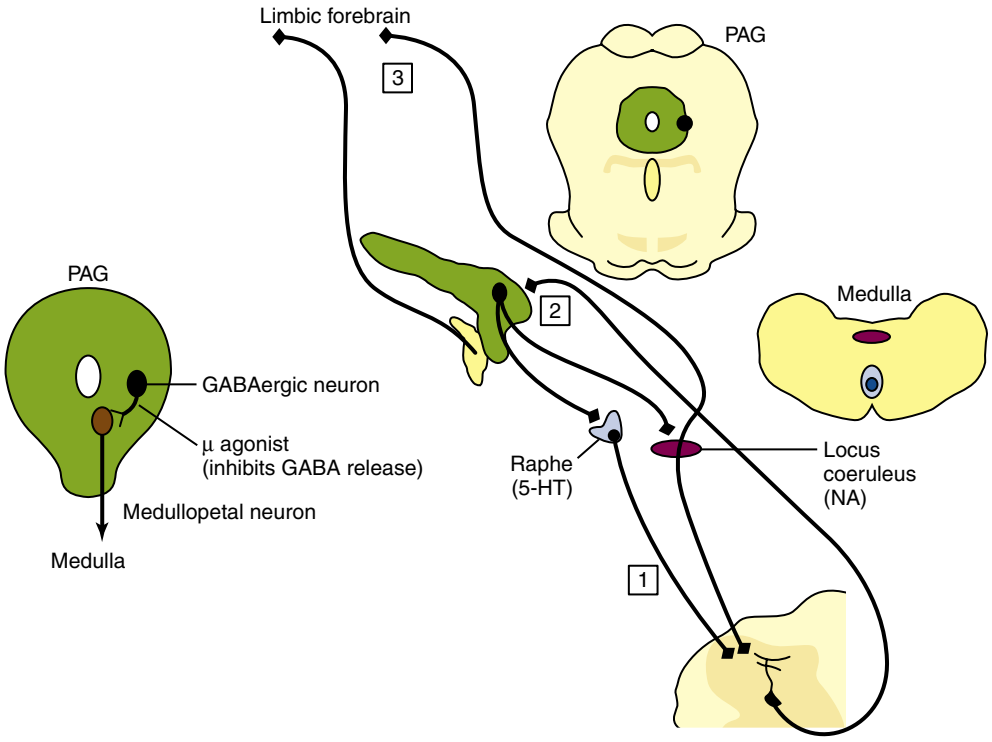
Several transmitters are known to be contained in and released from bulbospinal projecting pathways. However, the best characterized are the monoamines, norepinephrine, and serotonin.

Bulbospinal Norepinephrine

Norepinephrine projections to the spinal cord arise from lateral medullary sites and the locus coeruleus, whereas norepinephrine projections to the forebrain arise from the locus coeruleus (Fig. 9.8). Rostral projections are believed to play a primary role in altering the affective components of behavior. The caudal adrenergic projections play a principal role in regulating spinal nociceptive processing through action on spinal dorsal horn α_2-adrenergic receptors that are located presynaptic and postsynaptic to the primary afferent. Spinal delivery of α_2-adrenoceptor agonists, such as clonidine and dexmedetomidine, produces significant analgesia. The spinal action of an α_2-agonist is mediated by a mechanism similar to that used by spinal opiates. However, the receptor is distinct: (1) α_2 binding is presynaptic on C-fibers and postsynaptic on dorsal horn neurons, (2) α_2-receptors can depress the release of C-fiber transmitters, and (3) α_2-agonists can hyperpolarize dorsal horn neurons through a G_i-coupled potassium channel.

Bulbospinal Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) arises from the nucleus raphe magnus, which projects spinally, and from the raphe dorsalis, which provides the principal source of 5-HT in the forebrain. As reviewed earlier, spinipetal 5-HT projections can have multiple effects, including excitation and inhibition. These complex effects



• **Figure 9.8** Schematic of organization of opiate action within the periaqueductal gray (PAG) whereby μ-opiate actions block the release of γ-aminobutyric acid (GABA) from tonically active systems that otherwise regulate projections to the medulla and lead to activation of PAG outflow. (1) Excitatory outflow from the PAG activates bulbospinal projections that release serotonin (5-hydroxytryptamine [5-HT]) or noradrenaline (NA), or both, at the spinal level. (2). Preterminal opiate binding within the PAG on the ascending spinofugal projection. (3) Outflow from the PAG increases excitability of the dorsal raphe and locus coeruleus, from which ascending serotonergic and noradrenergic projections originate and project to the limbic forebrain.

suggest that under certain conditions, increasing the spinal 5-HT tone may *facilitate* nociceptive processing.

Altering Terminal Monoamine Concentrations

Notably, agents that regulate the extracellular concentrations of these monoamines can have pronounced effects on emotional tone and nociceptive transmission. Because extracellular levels depend not only on release but also on their reuptake, agents that block the reuptake transporter, such as tricyclic anti-depressants, can have analgesic properties. Current evidence suggests that analgesic actions are largely mediated through an effect on norepinephrine and not serotonin. This difference in their relative contributions to analgesic efficacy may reflect several opposing effects associated with the action of serotonin.

Nerve Injury Initiated Signaling and Pain

From the preceding sections, it was evident that the events that occur following peripheral tissue injury can lead to potent facilitation of neuraxial processing, which results in a large part of the persistent small afferent traffic that occurs with injury and inflammation. These changes reflect events that occur in the injured nerve (as reviewed in the preceding section): alteration of protein expression leading to upregulation of some proteins and downregulation of others. The increased spontaneous activity arising from neuromas and DRGs provides a tentative explanation for the ongoing dysesthesias associated with various nerve injury conditions. The prominent finding is that low threshold tactile stimulation acquires an aversive component that appears to present a more complex set of events. Current thinking is that it is mediated by low threshold mechanosensitive (Aβ) afferents. The precise mechanism of this involvement of low threshold afferents in the initiation of pain is not known, although several possibilities have been considered credible.

Crosstalk Between Large and Small Afferents

Following nerve injury, "crosstalk" mediated by ephaptic contacts may develop between afferents in the DRGs and neuromas. Here, depolarizing currents in one axon would generate a depolarizing voltage in an adjacent quiescent axon. In this manner, a large low threshold afferent drives the activity in an adjacent high threshold afferent.

Large-afferent Sprouting

As reviewed previously, large myelinated (Aβ) afferents project into the spinal Rexed lamina III and deeper. Small afferents (C-fibers) tend to project into spinal laminae I and II, a region populated by neurons responding to this high threshold input. It has been argued that following peripheral nerve injury, the central terminals of myelinated afferents (A-fibers) sprout into lamina II of the spinal cord. With this synaptic reorganization, stimulation of low threshold mechanoreceptors (Aβ-fibers) could produce excitation of these neurons and be perceived as painful. The degree to which this sprouting occurs is a point of the current discussion, and even though it does appear to occur, it is considerably less prominent than initially reported.

Loss of Intrinsic Inhibitory Control

A large number of small interneurons lie in the superficial dorsal horn; these interneurons contain and release GABA and glycine. As reviewed earlier, these terminals are presynaptic to the large central afferent terminal complexes and form reciprocal synapses, and GABAergic axosomatic connections have been identified in second-order and projection neurons (Fig. 9.6). Accordingly, these transmitters exert powerful inhibitory control over the activity of Aβ primary afferent terminals and second-order neurons in

the spinal dorsal horn. As discussed earlier, the importance of this local inhibitory circuitry is indicated by the observation that intrathecal delivery of a $GABA_A$ receptor or glycine receptor antagonist evokes a powerful tactile allodynia. Such observations led to the hypothesis that nerve injury may induce a loss of GABAergic and glycinergic neurons. Although some data support the loss of such neurons, this loss appears to be minimal. Recent observations suggest a second alternative. After nerve injury, spinal neurons are altered so that GABAA and glycine receptor activation become excitatory. As noted previously, these receptors are chloride ionophores. When these ionophores are activated, chloride moves according to the transmembrane gradient. The transmembrane gradient is maintained by transporters that export chlorides. After nerve injury, the activity of the chloride transporter is reduced, which leads to an increase in intracellular chloride and an increase in membrane Cl– conductance, as occurs with $GABA_A$ receptor activation, resulting in membrane depolarization. Thus paradoxically, afferent inputs that activate $GABA_A$/glycine channels may facilitate membrane depolarization and lead to a significantly enhanced response to the Aβ drive.

Enhanced Excitatory Drive

Glutamate Release

Spinal glutamate release plays an important role in post–nerve injury pain states. There is a significant enhancement in resting spinal glutamate secretion after nerve injury. This release is in accordance with (1) increased spontaneous activity in the primary afferent and (2) loss of the intrinsic inhibition that may serve to modulate resting glutamate secretion (see below). Several observations emphasize the significance of this release: (1) intrathecally delivered glutamate evokes powerful tactile allodynia and thermal hyperalgesia through the activation of spinal NMDA and non-NMDA receptors. (2) Spinal delivery of NMDA antagonists has been shown to attenuate hyperpathic states arising in animal models of nerve injury. NMDA receptor activation mediates the facilitation of neuronal excitability. In addition, the NMDA receptor is a calcium ionophore, which, when activated, leads to prominent increases in intracellular calcium levels. The increase in intracellular Ca^{2+} initiates a cascade of events, including the activation of a variety of enzymes (kinases), some of which phosphorylate membrane proteins (e.g. calcium channels and NMDA receptors) and others, such as the MAPKs, which mediate intracellular signaling, thereby leading to the altered expression of a variety of proteins and peptides (e.g. COX and dynorphin). Several factors have been shown to enhance glutamate release. Two examples are discussed below.

Spinal Dynorphin

Nerve injury leads to a prominent increase in spinal dynorphin expression. Intrathecal delivery of dynorphin can initiate the concurrent release of spinal glutamate and potent tactile allodynia; NMDA antagonists reverse this effect. Although dynorphin is an endogenous opioid peptide, these effects appear to be independent of any action on an opiate receptor.

Altered Channel Expression

As reviewed previously, nerve injury leads to the upregulation of various sodium channels and downregulation of potassium channels. This altered expression is referred to as the *neonatal phenotype.* This assertion belies the enormous changes in channel expression associated with nerve injury. For example, it has been shown that after nerve injury, there is a significant increase in the expression of the $\alpha_2\delta$ subunit. This subunit is found in the structures of several members of the voltage-sensitive calcium channel family. This binding site is densely present in the substantia gelatinosa of the superficial dorsal horn and DRG at the spinal level. The relevance of this increased expression is suggested by the potent anti-allodynic effects associated with the action of gabapentin. This molecule appears to exert its effects by highly selective binding to the $\alpha_2\delta$ subunit. N-type voltage-sensitive calcium channels also show increased expression, and spinal delivery of N-type calcium channel blockers such as ziconotide also produces potent anti-allodynic effects.

Non-neuronal Cells and Nerve Injury

As reviewed in the preceding sections, astrocytes and microglia have been shown to play a powerful constitutive role in increasing synaptic excitability through the release of a variety of active factors (Fig. 9.5). After nerve injury, significant activation of spinal microglia and astrocytes occurs in the spinal segments that receive input from the injured nerves. Work with TLRs suggests that products released centrally by nerve injury can activate these cells through constitutively expressed TLRs. This activation is manifested by morphologic changes in these cells and increased expression of cellular markers for microglia (e.g. OX42/p-p38 MAPK) and astrocytes (GFAP). Of particular interest is that in the presence of pathologies such as bone cancer, extravagant activation of these non-neuronal cells has been shown to occur. Although the origin of this activation is not clear, increased afferent traffic and release of excitatory transmitters and products that appear to be increased secondary to nerve injury, such as growth factors, appear to be involved. This activation of intracellular transcription factors serves to increase the spinal expression of COX, NOS, glutamate transporters, and proteinases and to downregulate other systems such as the chloride transporters discussed in the preceding section. Such biochemical components have been previously shown to play an important role in the facilitated state.

In addition to the role played by glia, there is also the appreciation that after injury, a variety of cell surface markers are expressed in the DRG that promote the migration of macrophages and neutrophils into the DRG. These cells are thought to contribute to the inflammatory milieu.

Adaptive immune signaling

As reviewed above, there is increasing evidence that autoimmune signaling may contribute to the appearance of facilitated states after nerve injury. Studies have shown that antibodies from patients displaying causalgic phenotypes (e.g. hyperpathia after nerve or tissue injury) given to mice can initiate a hyperpathic state in the animal and that patients where immune complexes have been removed may show improvements.

Supraspinal outflow

While the majority of this review has focused on the organization of the input/output function of spinal systems, it is evident that the manifestations of the pain experience occur because of the input into a higher-order system. Dorsal horn projection neurons (second-order neurons) relevant to the pain experience typically cross to ascend in the contralateral–ventrolateral quadrants of the spinal cord following two trajectories: (1) into the somatosensory thalamus, while the third-order neurons project to the somatosensory cortex (the classical somatosensory pathway),

and (2) to regions such as the parabrachial, medial, and ventromedial thalamus. Here, the third-order neurons project to various limbic forebrain (e.g. hippocampus, amygdala, anterior cingulate, and inferior insula). The first trajectory has properties that suggest encoding both the stimulus location and intensity. The second trajectory serves to innervate systems robustly associated with emotionality, affect, and the integration of memory and other sensory components (e.g. smell, hearing, vision). These systems provide the substrate for encoding the *sensory-discriminative* aspects of the pain phenotype, while the latter serves to integrate the emotionality and experiential components of the pain phenotype, which we refer to as the *affective motivational component*. Such circuitry would be considered to underlie the strong emotional component that a pain stimulus can evoke.

Overview

In summary, the post–tissue injury pain state reflects sensitization of the peripheral terminal in response to the local release of a variety of factors that initiate spontaneous activity and sensitization of the peripheral terminal. There is also a potent central (spinal) sensitization that leads to enhanced responsiveness of dorsal horn neurons that receive ongoing small afferent traffic. This condition results in an enhanced response to input from the injured receptive field and enlargement of the peripheral fields, which can activate these neurons through originally ineffective subliminal input. The augmentation reflects the local synaptic circuitry (glutamate/SP) and the spinobulbospinal linkages (5-HT) and by-products released from local non-neuronal cells. Afferent activation and sensitization are subject to regulation by various systems, including those that regulate the release of transmitters from the primary afferent and activation of second-order or projection neurons.

Regarding the events that occur after nerve injury, it is evident that there are two principal elements: those that account for spontaneous pain and those that lead to an alteration in the encoding of normally innocuous low threshold mechanical stimuli. Spontaneous activity is probably a reflection of the complex events that arise from channel expression and the inflammatory factors that appear after nerve injury and lead to ectopic activity. The alterations related to the facilitated response represented evident changes in the dorsal horn function. The net effect appears to be enhanced excitability secondary to the increased expression of excitatory elements and reduced inhibitory contribution. The increased excitation probably arises from several sources, including the activation of non-neuronal cells.

Finally, peripheral nerve injury, such as that caused by compression or trauma and chemotherapy, leads to a persistent pain state. In contrast, local tissue injury or inflammation results in hyperpathic states, with a time course parallel to the onset and resolution of the injury state. However, as reported in humans, the pain state originating from prolonged inflammation may persist even when the inflammatory state resolves (loss of neutrophils/macrophages and cytokines). Comparable pain states have been identified in pre-clinical models. Recognition of this propensity of an acute injury to transition to a persistent or chronic pain condition raises important issues regarding the convergence of mechanisms that underlie inflammatory and nerve injury conditions. For example, it is noteworthy that trophic and persistent changes in the DRG have been identified after long intervals (days to weeks) in animal models. In this case, transcription factors (e.g. ATF-3) are activated and show little tendency to reverse even over extended intervals. This suggests the possibility that in populations of patients and certain pre-clinical models, peripheral inflammation may lead to persistent changes in afferent neuraxial coupling. In studies involving TLR mutants, these changes in persistent pain and upregulation of transcription factors have been prevented. Other persistent changes were also identified. Importantly, this spinal encoding serves to encode the content of the message that is relayed to higher centers in the brain that serve to integrate the content with complex issues of emotion, affect, and learned experiences.

Key Points

- Aβ afferents, which are large, myelinated, fast-conducting axons, are typically activated by low-intensity mechanical stimuli. Aδ-fibers, which are smaller, myelinated, intermediate-conducting afferents, have subpopulations that preferentially respond to thermal or mechanical, low or high threshold stimuli. C-fibers, small unmyelinated, very slowly conducting afferents, are activated by high intensity thermal or mechanical stimuli (or both).
- With tissue injury, ongoing activity is initiated by changes in the local milieu that evoke activity and sensitize the peripheral terminal. With ongoing small afferent input, there is a spinal sensitization that reflects acute increases in neuronal responsiveness mediated by NMDA receptors and longer-term events reflecting activation of kinases, generation of pro-inflammatory intermediaries, and more persistent events mediated by transcriptional activation.
- After a chemical, immune, or mechanical injury to the nerve, afferent axons display (1) an initial burst of afferent firing, (2) electrical silence for an interval of hours to days, and (3) the appearance of "spontaneous" bursting activity in both myelinated and unmyelinated axons over hours to days. This ongoing activity reflects the initial dying back of the injured axon (retrograde chromatolysis) and the initiation of sprouting.
- Bulbospinal serotonergic projections act through excitatory 5-HT_3 receptors to enhance the firing of these lamina V neurons. These cells are noted for their ability to display a facilitated state called "wind-up." Blockade of this bulbospinal linkage or the use of 5-HT_3 inhibitors has been reported to reduce this facilitated state.
- It has been demonstrated that behavioral models of facilitation wherein the injury is conducted under a systemic anesthetic (e.g. barbiturate, volatile agent) show that the hyperalgesic state may be initiated. However, the injury is inflicted under the influence of an anesthetic.
- Though preventing the ascending pain message, anesthetics surprisingly do not appear to block the facilitatory processes that are initiated by small afferent input, probably at the level of transmitter release at the first spinal synapse.
- Prostaglandins act on a number of eponymous receptors located *presynaptically* on the primary afferent terminal and *postsynaptically* on second-order neurons.
- Following peripheral nerve injury, ongoing pain appears to represent ectopic activity in the neuroma and the DRG, a phenomenon reflecting upregulation of sodium channels and the expression of receptors activated by changes in the local milieu. The enhanced response to low threshold stimulation

may reflect the loss of intrinsic GABA and glycinergic inhibition and activation of non-neuronal cells.
- Current work increasingly points to the role of circulating autoantibodies that can interact with membrane channels and receptors, leading to their disablement and creation of a facilitated state or to classical Fcgamma receptors that can initiate signaling of afferents.
- The content of the ascending information arising from tissue and nerve injury is provided to supraspinal systems that integrate that information arising from the somatic and visceral body with the rich tapestry of learned experience, emotion, and other sensory inputs.

The contents of this chapter on the pharmacology of the substrates activated after tissue injury and nerve injury must be considered a broad overview. More detailed considerations and citations can be found in the detailed reviews listed below.

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10 Neuroimaging Techniques

MATHIEU ROY, ÉTIENNE VACHON-PRESSEAU, MARKUS PLONER, ARIANA M. NELSON

Introduction

Pain, defined as the conscious subjective experience associated with real or potential tissue damage,[1] is a product of coordinated activity across large portions of the brain.[2] In contrast, the concept of nociception refers to the objective neural processes triggered by nociceptive stimuli and does not imply consciousness. Therefore one important goal of neuroimaging is to understand how nociception leads to pain and explain what happens when pain appears to be dissociated from nociception, as observed in many chronic pain syndromes. This chapter discusses the non-invasive imaging modalities that can depict the structural and functional central nervous system (CNS) features associated with experimentally induced and chronic pain. The main objective of this chapter is to survey the brain imaging literature on these highly prevalent functional chronic pain syndromes, for which it is difficult to identify a clearly defined pathology. A more in-depth treatment of radiologic imaging techniques routinely used to identify CNS damage can be found in Chapter 20.

An overview of the most commonly used neuroimaging modalities can also be found in Box 10.1, where we briefly survey the techniques routinely used to identify damage to the CNS, as well as functional techniques that can assess CNS activity as a function of experimentally induced or chronic pain, which will be the focus of this chapter. We will begin with a brief historical overview of functional magnetic resonance imaging (fMRI) studies of acute experimentally induced pain before examining how chronic pain differs from pain evoked by nociceptive stimuli. We will then turn to positron emission tomography (PET) studies of endogenous opioidergic and dopaminergic systems in chronic pain syndromes. Finally, we will review recent electroencephalographic (EEG) studies of acute and chronic pain. Overall, this chapter should provide the reader with a good overview of the cerebral underpinnings of pain, as well as how this knowledge may have contributed to change our conception of pain and how it could be harnessed to guide certain clinical decisions.

Brain Imaging of Acute Experimental Pain

Brain Mapping

The study of the cerebral correlates of pain began with the investigation of patients with brain lesions causing abnormal pain perception.[3,4] The main conclusion from these studies was that pain was principally perceived in the thalamus, with a limited role in the cortex. However, as neurophysiologists began to follow the projections of nociceptive pathways up to the brain, the role of cortical structures in pain perception has gradually become more important.[5–8] With the advent of functional neuroimaging techniques in the late 1980s—first PET and then fMRI—researchers became endowed with a means to non-invasively probe the human brain in search for areas responding to noxious stimuli. Using these techniques, several studies found that high-intensity noxious stimuli (thermal, electrical, mechanical, or chemical) systematically produced more activity than low-intensity innocuous stimuli in a set of regions comprising the thalamus, anterior cingulate cortex (ACC), insula (Ins), primary and secondary somatosensory cortices (S1 and S2), and prefrontal cortex (PFC) (Fig. 10.1).[9,10]

Inspired by Ronald Melzack's terminology,[11] researchers soon started to refer to this collection of brain regions as the "pain matrix."[12,13] Melzack's original "Neuromatrix" theory of pain proposed that the conscious experience of pain was generated by the flow of activity within a widespread network of convergent/divergent loops between the thalamus, cortex, and limbic system. He thought that the general function of this network, which he called the "body-self neuromatrix," was to produce a unified representation of the body and self. Moreover, he suggested that the various bodily states generated by the neuromatrix each had a particular "neurosignature" (i.e. a characteristic pattern of neuronal activity stemming from the interaction between environmental inputs and the pre-existing state of the neuromatrix). Therefore according to Melzack, there is no "pain center" in the brain, but rather a general-purpose "body-self neuromatrix" capable of representing a wide array of bodily states, of which pain is just one particular example. Eventually, Melzack's idea of a "body-self neuromatrix" was simplified, and the term "pain matrix" began to be used to refer to the brain regions generally activated by pain.

Discussions in the field revolved around how different regions of the "pain matrix" contributed to the unified pain experience. An important distinction was made between the sensory dimension of pain, reflecting the location, intensity, and sensory quality of the experience, and the affective dimension reflecting the intrinsic unpleasantness of pain.[14] The sensory dimension of pain is thought to result from activity in the cerebral targets of the lateral spinothalamic system: ventral posterior (VPI) and ventral posterior lateral thalamic nuclei, S1, S2, and posterior insula (pINS). Studies of patients with brain lesions confirmed that damage

• BOX 10.1 Overview of Neuroimaging Modalities

Neuroimaging techniques are defined by the obligatory processing of the data after acquisition to be interpreted visually as an image by a human clinician. The amount of processing required for the following imaging modalities is listed in approximately ascending order, starting with plain radiographs, which is the only modality that does not absolutely require processing.

Radiographs (XR): Penetrating ionizing radiation is used to distinguish radiopaque tissues from those that are radiolucent in a two dimensional view. Although simple radiographs of the cerebrum and spinal column can be used clinically to evaluate structural abnormalities in the osseous structures that house neural pathways, they do not reveal disruption of the neural soft tissues. These are most often used clinically to evaluate injury following trauma or to assess prior surgical interventions for hardware integrity and osseous fusion.[175]

Computed Tomography (CT): Tomography is defined as an image produced by a penetrating wave, and in medicine, CT scans are a fast and relatively inexpensive method of imaging the brain and spinal cord. Although CT can visualize solid or aqueous structures with much higher resolution than a plain radiograph, it is still difficult to discern the characteristics of the soft tissues, and the amount of post-processing that can be conducted is limited. Resolution can be improved by the addition of intravenous or intrathecal contrast. The use of CT with intrathecal contrast is most commonly used when patients have spinal hardware *in situ*, which obscures the relevant anatomy under MRI.[176]

Positron electron tomography (PET): This 3D imaging modality uses intravenous radionuclide tracing to assess tracer uptake in different organs or estimate neurotransmitter activity or receptor availability for ligands (e.g. opioids).[177] Once taken up by tissues, the tracer decays into positrons that react with electrons in the body and emit photons. This is detected by sensors, and the processed images are often coupled with CT to form clinically relevant images and have recently been paired with magnetic resonance for improved resolution.[178]

Magnetic resonance imaging (MRI): Structural MRI evaluates the white matter, gray matter, and cerebrospinal fluid of the cerebrum and spinal cord. In the presence of the magnet, the random motion of atoms within the body is brought into alignment. The radiofrequency coils of the MR machine produce a pulse of energy that slightly tilts the atoms away from their original alignment with the magnetic field. As they recess back to their original orientation, they emit a pulse of energy, which is captured by sensors and processed into an image.[179] MRI can be used to form images with or without the use of paramagnetic contrast dye, and indications for contrast include suspicion for metastasis or hardware *in situ* that will cause non-contrast MRI to obscure relevant anatomy.[180] Most MR machines in clinical use are those with a 1.5 Tesla or 3 Tesla magnetic field, with a higher Tesla strength correlating to higher image resolution.[179]

T1 sequence: The spin-echo (T1) sequence is clinically preferred for MR studies with contrast in evaluation of perfusion of spinal tissues, most commonly to assess primary tumors for vascularization, indicative of high tumor grade, or to evaluate metastases for vascularity that would be amenable to endovascular ablation. It is also used for cerebral imaging in the evaluation of neurologic disorders and supratentorial lesions.

T2 Sequence: Fast spin-echo (T2) is the most common MRI sequence examined by pain physicians evaluating spinal anatomy. In this sequence, the tissues with high water content (e.g. the cerebrospinal fluid) are white/bright on the image, making areas of spinal stenosis or disc herniation highly visible.

STIR: Short tau inversion recovery has higher sensitivity but lower specificity than other conventional sequences in assessing spinal abnormalities because of infectious or neoplastic etiology in the spinal column. Clinically, this is most useful in the evaluation of the spinal cord for multiple sclerosis lesions,[181] and in the vertebral bodies for compression fractures.[182]

FLAIR sequence: The fluid attenuated inversion recovery (FLAIR) sequence is a further modification of the traditional spin-echo (T2) technique that suppresses the CSF signal and minimizes the contrast between gray and white matter. This improves the detectability and visibility of pathologic lesions adjacent to the CSF. This sequence is considered more sensitive in the evaluation of ischemia, neoplastic disease, and multiple sclerosis in the neuraxis.[183]

Angiography: Both CT and MR angiography can be used to assess spinal blood supply for surgical planning or in the diagnosis of vascular pathologies, such as spinal dural arteriovenous fistulas.[181]

Advanced MRI Techniques

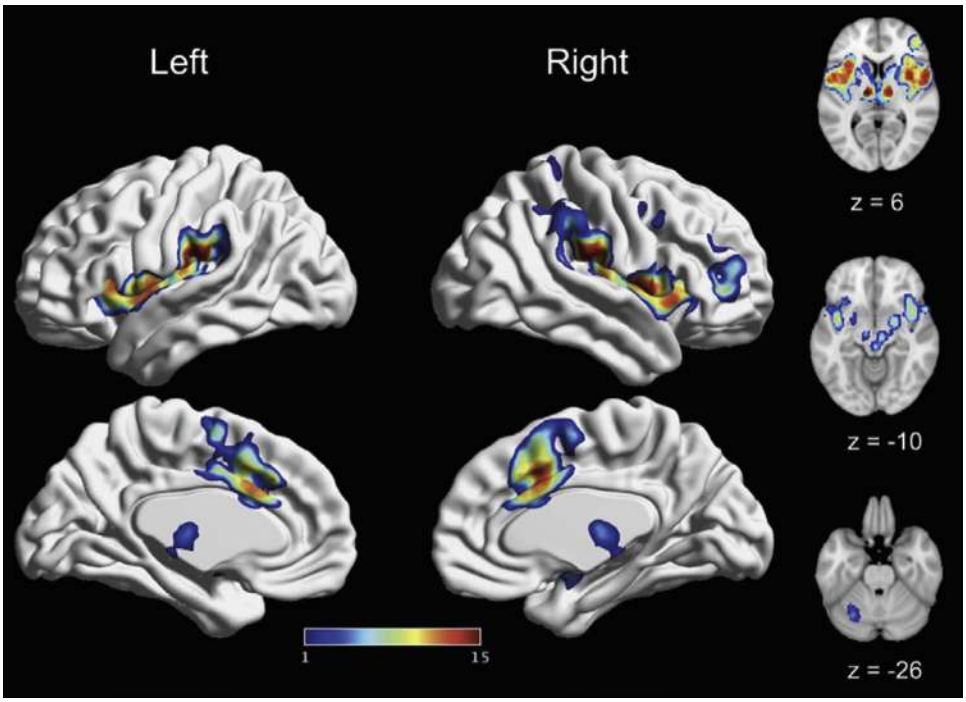
Functional MRI (fMRI) and diffusion MRI (dMRI) have been increasingly used in research studies targeting acute and chronic pain populations. These methods represent the only objective method of measuring the subjective experience of pain, as it changes the mentation of the individual. Although these techniques show great promise in future clinical applications, at the time, they are purely used in investigational pursuits.

fMRI: fMRI involves the acquisition of T2*-weighted images of the brain that are sensitive to the proportion of oxygenated and deoxygenated hemoglobin (also called BOLD signal), which is related to brain activity. In *task-based fMRI*, experimental pain stimuli (thermal, mechanical, electrical, or chemical) can be repeatedly administered to participants for several tens of minutes. The general linear model is then used to estimate the amplitude of the hemodynamic response function, which is the influx of oxygen that follows neuronal activity in small parcels of the brain called voxels. Each voxel had a volume of approximately 8-64 mm^3. A typical $3 \times 3 \times 3$ mm voxel (27 mm^3) contains about 5.5 million neurons.[184] In *resting state fMRI* (rs-fMRI), participants are scanned while still lying in the scanner for periods of 5–30 min or more. Then, correlations in the time series of functional images can be computed for one or several pairs of brain regions to assess their functional connectivity. Finally, in *ASL*, brain perfusion is measured by "tagging" water molecules with a radiofrequency pulse in certain slices of the brain and then tracking them as they release their energy in other regions of the brain. Therefore ASL can track metabolic activity related to more diffuse states such as chronic pain, but one current problem is its relatively low signal-to-noise ratio.[185]

Diffusion-weighted imaging (DWI): DWI measures the diffusion of water molecules in the brain. Diffusion tensor imaging (DTI), a special type of DWI, has been used extensively to map white matter tracts in the brain. Metrics derived from DTI include mean diffusivity (MD), which is the degree to which water diffuses at each location, and fractional anisotropy (FA), which is the coherence of this diffusion in a particular direction.[186]

to S1/S2 produces impairments in perceiving the intensity and location of pain.[15] Moreover, the parieto-opercular region, which encompasses S2 and pINS, seems to be particularly important for pain. Not only is activity in that region relatively specific to pain,[16] but it is also the only region of the brain where brain stimulation can occasionally provoke painful sensations.[17] However, without further activation of other brain regions associated with affective feelings, activity in these sensory regions does not appear sufficient to produce a full-blown pain experience.

Indeed, nociceptive sensations must also be perceived as unpleasant to really be considered as pain. The affective dimension of pain is thought to depend on activity in the cerebral targets of the medial spinothalamic pathway: the medio-dorsal thalamic nucleus, ACC, and anterior Ins (aINS). Lesions in the ACC, or of the white matter tracts connecting it to the operculo-insular cortex, can produce a condition called pain asymbolia, whereby nociceptive sensations seem to be devoid of negative affect.[18] Finally, activity in the aINS is generally ascribed to interoception, that is, the constant monitoring of the internal state of the body in the service of homeostasis,[19] which includes pain but also other imperative sensations such as hunger or thirst.[20] In addition to activity in core "pain matrix" regions (thalamus, S1, S2, ACC, insula), brain imaging studies of acute experimental pain have often reported activation in several other regions of the brain such as



• **Figure 10.1** Brain regions consistently associated with experimentally induced pain. Results of a 2020 meta-analysis of 200 fMRI studies. The value assigned to each voxel reflects the number of main effects analyses, in which it was reported to be significant. The most consistently activated areas included the bilateral thalamus, bilateral insula, bilateral SII, and bilateral MCC. Adapted from Xu et al.[9]

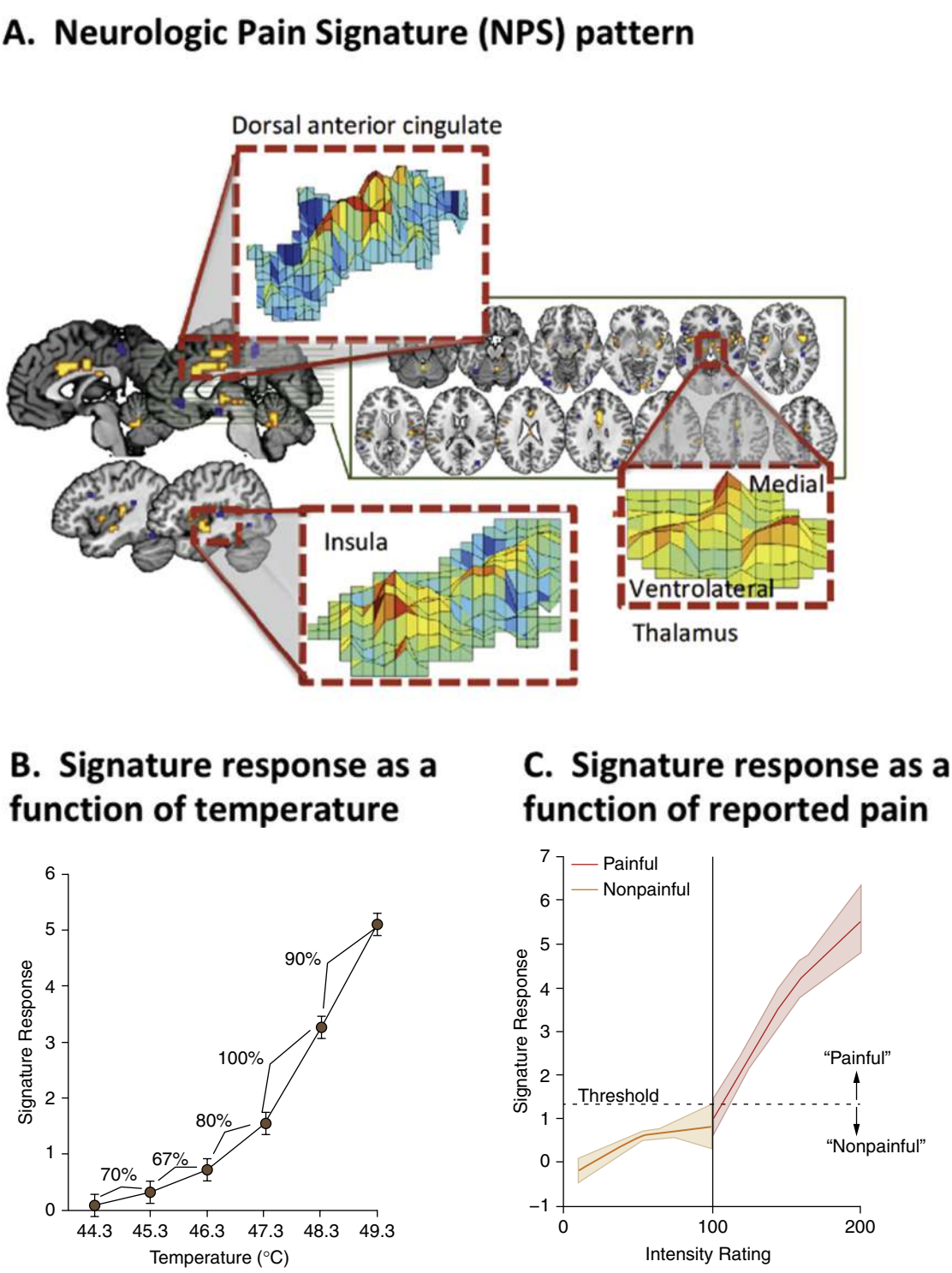
the brainstem (BS), amygdala, hippocampus, and prefrontal cortex (PFC).[9] Activity within these regions tends to be interpreted as either reflecting non-experiential aspects of pain, such as learning or autonomic regulation, or post-experiential processes not specific to pain, such as secondary appraisals and action selection. Therefore an important distinction in the field was between a primary pain effect that would be specific and intrinsic to the pain experience, and a secondary pain effect that would be more optional and the result of secondary appraisals about the significance of pain for oneself.[14]

Problem of Specificity and Multivariate Approaches

The concept of the "pain matrix" soon became criticized based on its lack of specificity. Because of its nature, pain results from excessive somatosensory stimulation. Accordingly, brain imaging studies of acute experimental pain have capitalized on the difference between high- and low-intensity stimulation to track regions responding to pain. However, this means that activity in these regions can also be interpreted as reflecting the perceptual salience of high-intensity stimulations, which may or may not be specific to pain. By comparing the patterns of activity elicited by visual, auditory, and tactile non-painful and painful heat stimulations, Mouraux et al.[21] concluded that most regions of the "pain matrix," such as the Ins and ACC, responded to the salience of external stimulation and were not specific to pain.

It is only with recent advances in machine learning that more accurate and fine-grained multivariate pain-predictive patterns could be devised.[22] Machine learning departs from traditional statistics by assessing the prediction accuracy on a different subpartition of the data than that used for developing the predictive model. From this perspective, predictive models can be said to be "trained" to minimize their out-of-sample error, thereby maximizing the prediction accuracy for new unseen data points.[23] This makes machine learning an ideal technique for optimizing the predictions of individual patients. Before being applied to pain, machine learning has already been used in cognitive neuroscience to make different types of predictions based on patterns of brain activity, such as identifying which letters participants are seeing[24,25] or the content of their dreams.[26] Using a similar approach, Wager et al.[27] developed an fMRI-based brain signature to predict the pain produced by thermal stimuli of different intensities (Fig. 10.2). This signature pattern, called the neurologic pain signature (NPS), also proved to be highly sensitive to the presence of diverse types of pain in new individuals tested on different scanners. The NPS also distinguished pain from other salient and unpleasant events, such as social rejection,[28] or vicarious pain.[29] Finally, although the NPS was shown to be highly sensitive to pain caused by the intensity of noxious inputs, it appeared to be insensitive to the impact of psychological interventions, such as cognitive self-regulation.[30]

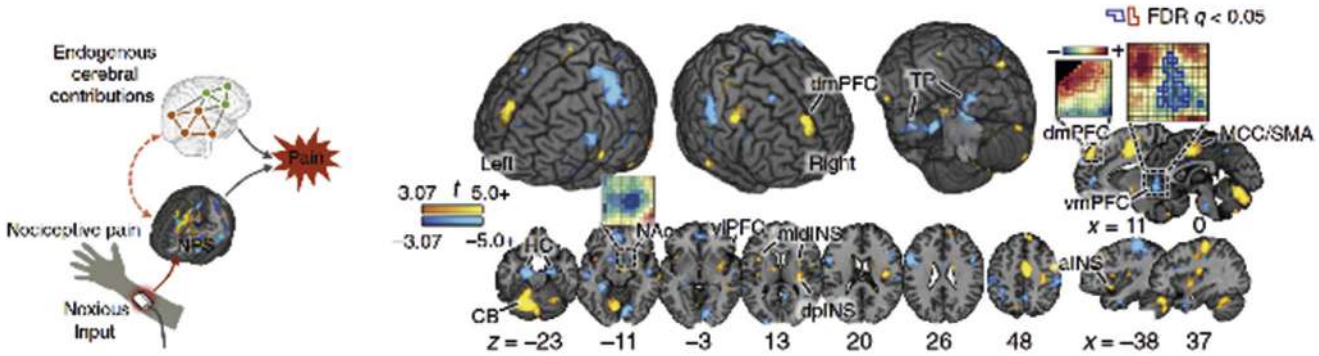
To capture the additional, non-nociceptive source of variation in pain ratings, a second signature was trained to predict pain after controlling for stimulus intensity and NPS pattern expression. The resulting signature, called the stimulus intensity independent pain signature (SIIPS; Fig. 10.3), was shown to explain approximately 16% of the variation in pain ratings for single pain trials, which is comparable to the variance explained by the NPS. When combining both signatures, predictions account for 25% of the explained variance for single trials and over 80% of the explained variance when averaging over several trials. Eventually, other signatures were also trained to predict social rejection,[28] vicarious pain,[29] negative affect,[31] and various other subjective experiences related to pain.[32]



• **Figure 10.2** Neurologic Pain Signature (NPS). A, The NPS pattern. The map shows weights that exceed a threshold (false discovery rate of q<0.05) for the display. Insets stress the importance of multivariate patterns in the three key regions. Adapted from Zaki et al. (2016).[172] B and C, In a separate study, the NPS signature response score tracked the temperature of the stimulation (percentages represent discrimination accuracies between pairs of adjacent temperature levels), as well as subjectively reported pain (100 = pain threshold). Adapted from Wager et al.[27]

Therefore it seems possible to use measures of brain activity to predict the presence of pain or other phenomena closely related to pain.

This new multivariate approach also marks a departure from traditional brain mapping grounded in systems neuroscience. Indeed, instead of tracking pathways that convey nociceptive information from the periphery to the brain, the goal is to identify the patterns of brain activity that may give rise to our subjective experiences of pain. One interesting avenue for understanding mind-brain relationships comes from the field of emotion research, where more recent theories of emotional feelings have stressed the concept of



• **Figure 10.3** Stimulus Intensity Independent Pain Signature (SIIPS). The SIIPS was developed to model endogenous cerebral contributions to pain beyond nociception. Some of the cerebral contributions may interact with nociceptive brain systems (red nodes), whereas others contribute to pain independent of nociceptive processing (green nodes). *Right*, the SIIPS pattern, which is predictive of residual pain ratings after removing the effects of stimulus intensity and NPS response. The map shows thresholded voxel weights (at q<0.05, false discovery rate [FDR]). Some examples of unthresholded patterns are presented in the insets; small squares indicate the individual voxel weights. *aINS*, Anterior insula; *CB*, cerebellum; *dmPFC*, dorsomedial PFC; *dpINS*, dorsal posterior insula; *HC*, hippocampus; *MCC*, mid-cingulate cortex; *midINS*, middle insula; *NAc*, nucleus accumbens; *SMA*, supplementary motor area; *TP*, temporal pole; *vmPFC*, ventromedial PFC; *vlPFC*, ventrolateral PFC. Adapted from Woo et al.[171]

"degeneracy."[33] Degeneracy refers to the idea that there may be a many-to-one mapping between brain activity and subjective experiences. This suggests that the same subjective experience, such as pain, may be caused by different patterns of brain activity on different occasions.[34] However, this not mean that *any* pattern of brain activity could produce pain, but rather that there can be substantial variation within a restricted set of possibilities. This is what Melzack had initially proposed, and recent research on pain neurosignatures supports this. We may need to abandon our search for a one-to-one mapping between pain and a specific pattern of brain activity, as this concept is likely fundamentally flawed.

Brain Imaging of Chronic Pain

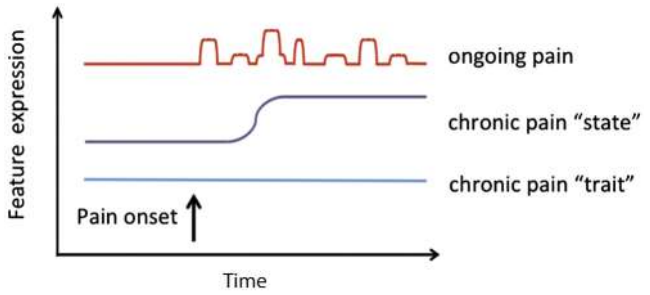
Chronic pain is usually defined as pain lasting for more than six months.[35] It comprises many clinical conditions that can differ on several dimensions: etiology, location, temporal characteristics, intensity, quality, and whether the pain is spontaneous or evoked by certain activities. One important puzzle for clinicians and researchers is that peripheral markers of disease often do not predict subjectively reported pain and associated disability, as observed in osteoarthritis (OA), chronic low back pain (CLBP), or fibromyalgia (FM).[36] Therefore researchers have focused on brain imaging to examine the role of the CNS in the maintenance of chronic pain.

Evoked Pain and Hyperalgesia

The first brain studies of chronic pain were set out to examine the brain activity of patients with chronic pain in response to noxious stimuli. While some studies seem to confirm the idea that certain chronic pain syndromes may be associated with a hyperalgesic state, it is difficult to draw a firm conclusion from these studies.[37–49] One problem is that flexibility in the list of regions comprising the "pain matrix" may have rendered the hypothesis of increased activity in the pain matrix difficult to falsify.[50] Still, it is fair to assume that the cerebral processing of nociceptive stimuli can be influenced by the state of the brain that receives these noxious inputs.[51] In a pioneering study, Baliki et al.[52] found that patients with CLBP have reduced nucleus accumbens (NAc) responses to painful stimulus offset. More recently, Callan et al.[53] used machine learning techniques to classify CLBP versus healthy controls with 92.3% accuracy based on their brain responses to painful electric shocks. Interestingly, brain responses to nonpainful stimuli can sometimes differentiate patients from controls. For instance, it has been proposed that patients with FM also experience multisensory hypersensitivity. Consequently, brain responses to stimuli from other sensory modalities, such as visual stimuli, can be used to distinguish patients with FM from healthy controls with 82% accuracy.[54] Moreover, combining responses to visual and mechanical stimuli increases classification accuracy up to 93%, suggesting that there may be virtue in combining responses to different kinds of tasks or stimuli.[55] Altogether, this suggests that stimulation paradigms can potentially provide a way to classify patients based on their brain's response to external stimuli.

Chronic Pain "State" vs. "Trait"

Structural MRI. Several studies have observed various structural alterations in the brains of patients with chronic pain compared to healthy controls. In a meta-analysis of 23 early volumetric studies conducted prior to 2011 and covering over 15 different pain disorders, Smallwood et al. found that chronic pain was associated with decreased gray matter volume in more than 30 different brain regions, suggesting that chronic pain may be associated with a widespread decrease in gray matter volume.[56] However, one important recurring question is whether structural differences between patients and controls reflect premorbid traits associated with an increased risk of chronicity (chronic pain "trait"), or if they reflect relatively stable consequences of being subjected to constant uncontrollable pain (chronic pain "state").[57] One way of distinguishing between the two has been to track patients as they transition from acute/subacute (<three to six months) to chronic (>six months) pain. Any brain feature remaining stable throughout the transition likely represents a predisposition, whereas features changing as a function of the transition toward chronic pain might be more reflective of a chronic pain "state" (Fig. 10.4). Using this approach, Vachon-Presseau et al. found that small



• **Figure 10.4** Brain imaging can track different aspects of chronic pain. Different brain features (e.g. volume of a certain region or certain connectivity patterns) can track different aspects of chronic pain. Certain features can track the ongoing subjective feeling of pain, which typically fluctuates over time (red line). Other types of features can track the more diffuse state (purple line) associated with the prolonged presence of recurrent pain episodes. The chronic pain "state" reflects the consequences of pain and may take a certain amount of time to develop. Finally, certain features may reflect more stable "traits" that precede the onset of pain and may confer vulnerability to chronic pain.

hippocampus and amygdala volumes predicted the risk of transitioning from subacute to CLBP, suggesting that it may constitute a predisposition rather than a consequence of the pain.[58]

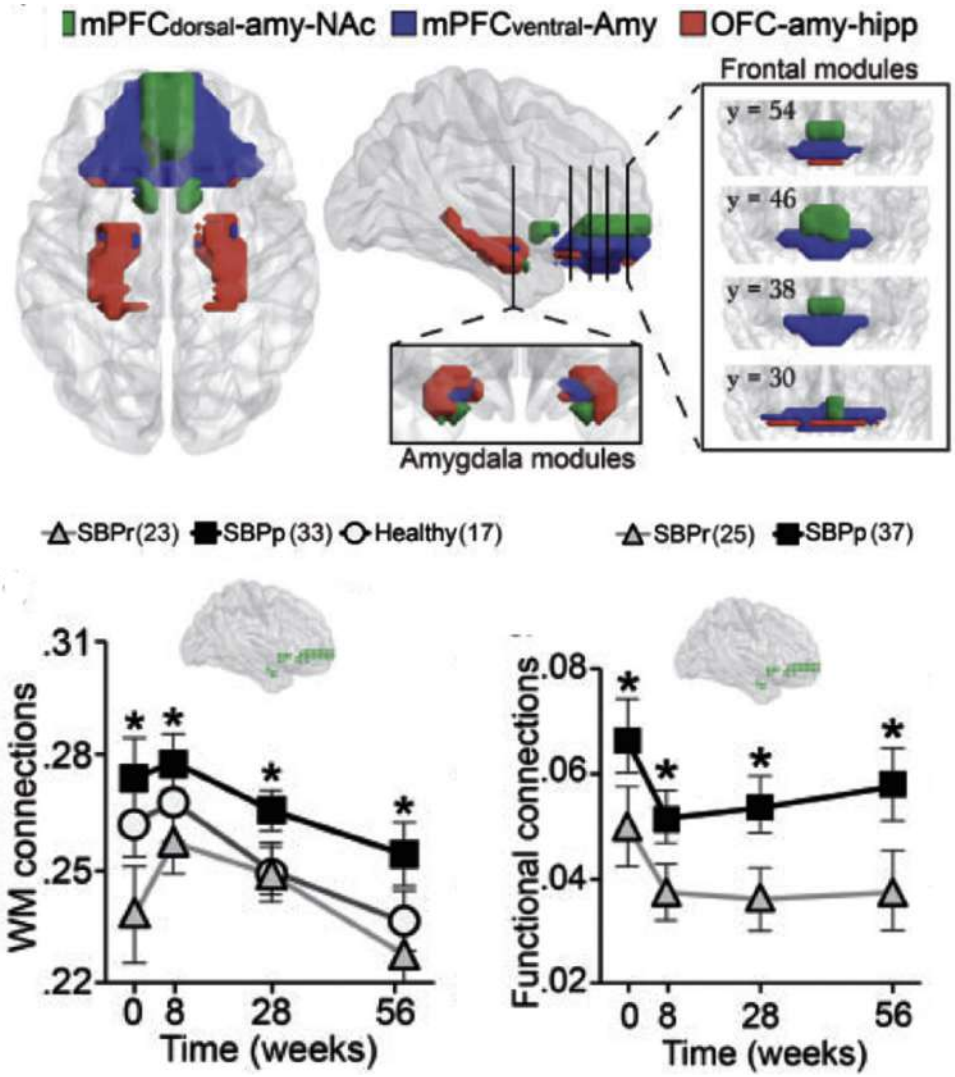
Another strategy used to disentangle chronic pain "trait" vs. "state" has been to track the impact of pain-relieving interventions on the brain: brain features associated with chronic pain "state" should come back to normal following successful pain treatments, whereas brain features associated with chronic pain "trait" should remain unchanged. Using this approach, Seminowicz et al. found that successful treatment with CLBP (surgery or facet joint injections) reversed thinning of the dorsolateral prefrontal cortex (DLPFC).[59] These findings were in part replicated in a study examining the effects of cognitive behavior therapy for CLBP, which also observed increases in DLPFC volume as well as in the volume of the hippocampus and several parietal and frontal areas.[60] Finally, the last approach to disentangle chronic pain state vs. trait could be to experimentally induce chronic pain, a procedure that can only be performed in animal models of chronic pain. Using this approach, Seminowicz et al.[61] found that a spared nerve injury (SNI) rat model of chronic pain was associated with thinning of the prefrontal, entorhinal, and retrosplenial cortices, corroborating the results obtained in patients. Altogether, these findings suggest that reductions in prefrontal brain volume associated with chronic pain could largely be a consequence rather than a cause of pain chronicity.

When using machine learning to devise structural brain signatures of chronic pain, prediction accuracies tend to remain relatively modest (i.e. between 70% and 76%). Moreover, predictive patterns differ widely between studies examining various chronic pain syndromes such as CLBP,[62] chronic pelvic pain,[63] FMS,[64] irritable bowel syndrome,[65] dysmenorrhea,[66] and migraine.[67] Alterations in the medial prefrontal and somatosensory cortices seemed to predominate in most predictive patterns. These findings are similar to those of the previously mentioned volumetric meta-analysis, which also reported a widespread reduction in gray matter in patients with different types of chronic pain.[56] A more parsimonious explanation of these findings could be that these diffuse alterations in gray matter reflect accelerated brain aging. This hypothesis was recently confirmed by applying a validated brain signature of aging to a sample of patients with chronic pain.[68,69] An important avenue for future research is to try to understand what drives these structural changes. As mentioned previously, rodent models of chronic pain could provide useful information for understanding structural brain changes resulting from chronic pain.[61]

Resting state connectivity While there has traditionally been sustained interest in the structural brain features associated with chronic pain,[56] the field has recently witnessed an important shift toward functional connectivity-based markers of chronic pain. This reflects a more general tendency in brain imaging studies of neuropsychiatric conditions, which have found that resting state connectivity data contain useful information for classifying various conditions such as Alzheimer's disease or schizophrenia.[22] During a resting state scan, blood-oxygen level dependent (BOLD) activity is measured while participants rest in the scanner, typically for durations of 5–30 min. Brain activity is then extracted from a hundred or so functional sub-regions of the brain, which are called parcels. Finally, the temporal time-course of BOLD activity in each parcel is correlated with all other parcels to produce connectivity maps or connectomes, which can be diagnostic of certain brain conditions. This approach has demonstrated that patients with chronic pain display increased connectivity between limbic structures (striatum, amygdala, hippocampus) and orbito- and medial prefrontal cortices (Fig. 10.5).[70,71] Moreover, these patterns of altered connectivity have been shown to be stable in time and to predict the transition from subacute to chronic pain, suggesting that they may reflect stable "traits" conferring a higher risk of developing chronic pain. One possibility could be that limbic-prefrontal connectivity predisposes individuals to various kinds of stress-related disorders, of which chronic pain is one instance.[50]

Similar connectivity-based signatures have also been developed for the diagnosis and prognosis of other painful conditions, such as functional dyspepsia,[72,73] rheumatoid arthritis, FM,[74] migraines,[75] neuropathic pain,[76] or chronic pelvic pain.[77] However, because these different studies employed different analytical techniques or tried to make slightly different predictions, it is difficult to draw any general conclusions regarding commonalities and differences between their findings. To identify predictive patterns that are common across pain conditions, Baliki et al. used the same analysis pipeline to directly compare predictive signatures for CLBP, OA, and complex regional pain syndrome (CRPS).[78] Altered connectivity between the mPFC, ACC, and insula was common to all conditions, consistent with the idea that it might reflect a more general vulnerability trait. In contrast, each condition was associated with a unique profile of altered connections with cortical areas that could reflect the disease-specific consequences of persistent pain. In support of this hypothesis, Mansour et al.[79] observed that CLBP, OA, CRPS, and a rodent SNI model of chronic pain all displayed a global disruption in brain connectivity patterns, which seems to follow the onset of chronic pain.

Finally, one of the most promising applications of brain imaging could be its use in precision medicine, that is, the customization of treatment as a function of the patient's individual characteristics. For instance, in the case of depression, Drysdale et al. used resting state fMRI (rsfMRI) to cluster depressed patients into four biotypes, one of which was associated with higher chances of successful treatment by transcranial magnetic stimulation.[80] In the case of pain, an early study by Wanigasekera and colleagues tried to predict opioid analgesia in a sample of healthy individuals subjected to painful thermal stimulation.[81] They found that trait reward responsiveness and brain responses to noxious stimuli in the rostral ACC, orbitofrontal cortex (OFC), amygdala, hippocampus, caudate, NAc, and ventral tegmental area predicted the effect of remifentanil



• **Figure 10.5** Functional and structural connections predicting transition from acute to chronic pain. *Top.* Modularity analysis performed on prefrontal-subcortical networks identified three sub-systems: (i) dorsal medial PFC-amygdala-nucleus accumbens (mPFCdorsal-amy-NAc); (ii) ventral medial PFC-amygdala (mPFCventral-Amy); and (iii) orbitofrontal cortex-amygdala-hippocampus (OFC-amy-hipp). *Bottom.* Functional and white matter connections in the mPFC-dorsal-amy-NAc sub-system differentiate subacute back pain patients who will remit (SBPr) from those who will persist (SBPp). Differences between SBPr and SBPp patients were present at time zero (duration of pain < six months) and remained stable over time. Adapted from Vachon-Presseau et al.[58]

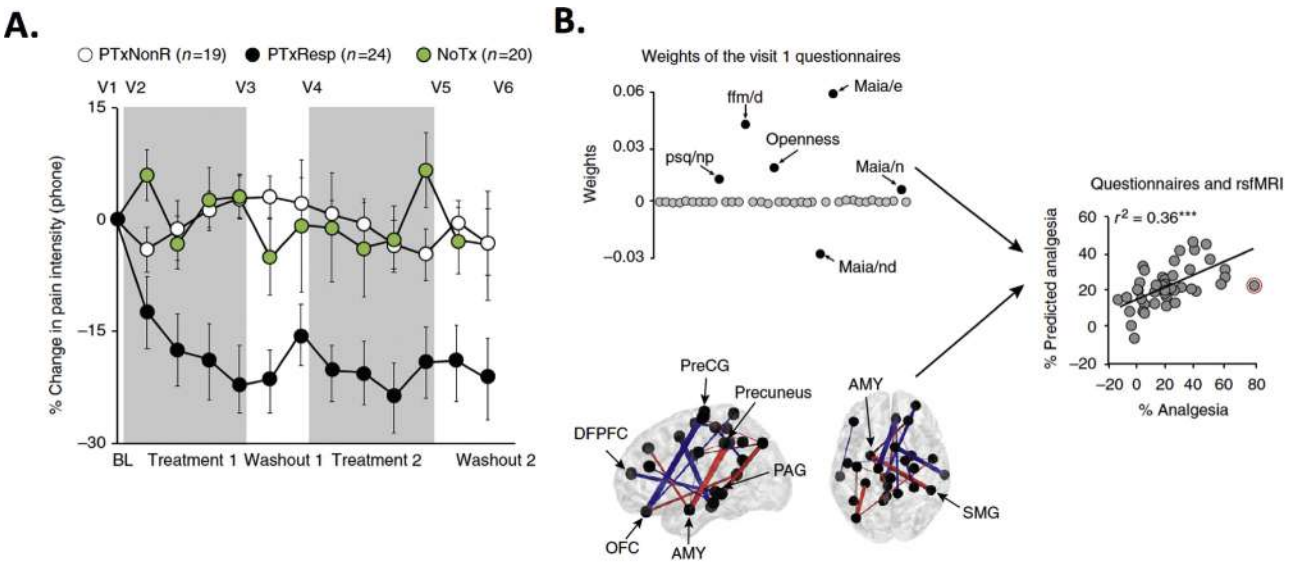
on thermal pain. More recently, Vachon-Presseau et al. combined questionnaire data and structural and resting state fMRI to predict placebo analgesia in a sample of patients with CLBP. They found that subcortical limbic volume asymmetry, sensorimotor cortical thickness, functional coupling of prefrontal regions, ACC, and periaqueductal gray (PAG), as well as psychological traits related to interoceptive awareness and openness, could predict the presence of a placebo effect with an accuracy of 0.72 (Fig. 10.6).[82] Importantly, brain imaging contributed predictive information that was not present in the questionnaire data and could therefore have an added value in precision medicine for chronic pain.

Ongoing Pain

The last important aspect of chronic pain that has proven particularly difficult to capture is the pain itself, that is, the ongoing feeling of pain that patients may experience at any given moment. In a recent study, Wasan et al. employed arterial spin labeling (ASL) to measure brain perfusion before and after CLBP patients engaged in "clinical maneuvers" (such as straight leg raises or pelvic tilts) designed to exacerbate patients' pain.[83] The pain produced by the maneuvers was associated with increased perfusion in the S1, S2, anterior insula, and medial and dorsolateral PFC. A relatively similar approach was recently used with resting state fMRI by Lee and colleagues.[84] They began by devising a connectivity-based signature that predicted the tonic pain state induced by the oral administration of capsaicin. Then, in the second step, they applied this tonic pain signature, or ToPS, to two other data sets of patients with CLBP and found that the ToPS could reliably distinguish patients from controls and predict subjectively reported low back pain (Fig. 10.7). This suggests that the ToPS was in part capturing the patient's ongoing back pain. The most reliable positive weights of the signature (i.e. higher pain with increasing connectivity) were found in the connections between the somatomotor network (SMN), the frontoparietal network (FPN), the visual network, and the dorsal attention network, which seems to suggest the importance of multisensory integration,[85] and top-down attention processes in tonic pain.[86] The most reliable negative weights (i.e. lower pain with increasing connectivity) were found in the limbic and paralimbic cortical regions (limbic network, LN) and BS, indicating the importance of context processing,[87] and the involvement of descending pain modulation.[88]

Positron Emission Tomography

PET is a brain imaging technique that uses radiolabeled tracers to measure brain metabolism or receptor availability. As mentioned above, the first brain imaging studies of pain used PET



• **Figure 10.6** Brain predictors of placebo analgesia. *Left.* Participants were administered a placebo pill for two periods of 14 days (treatment one and two in *gray*), each followed by a washout period of seven days (washout one and two in white). Placebo responders (*black circles)* displayed reduced pain over the course of the study compared with non-responders (*white circles*) or controls receiving no treatment (*green circles*). *Right.* Questionnaire data (top) and functional connectivity data (*bottom*) combined can predict 36% of the variance in placebo analgesia. In the top figure, *black dots* on the top represent questionnaires that significantly contributed to the prediction. *Maia*, Multidimensional assessment of interoceptive awareness; e, emotional awareness subscale; n, noticing subscale; nd, not distracting subscale; ffm/d, five-facet mindfulness/description; psq/hp, pain sensitivity questionnaire/high pain; openness, openness subscale from the NEO Five Factor Inventory. In the bottom graph, the *blue lines* represent negative functional links, and the *red lines* represent positive functional links. *OFC*, Orbitofrontal cortex; *DLPFC*, dorsolateral prefrontal cortex; *AMY*, amygdala; *PAG*, periaqueductal gray; *PreCG*, precentral gyrus; *SMG*, supramarginal gyrus. Adapted from Vachon-Presseau et al.[82]

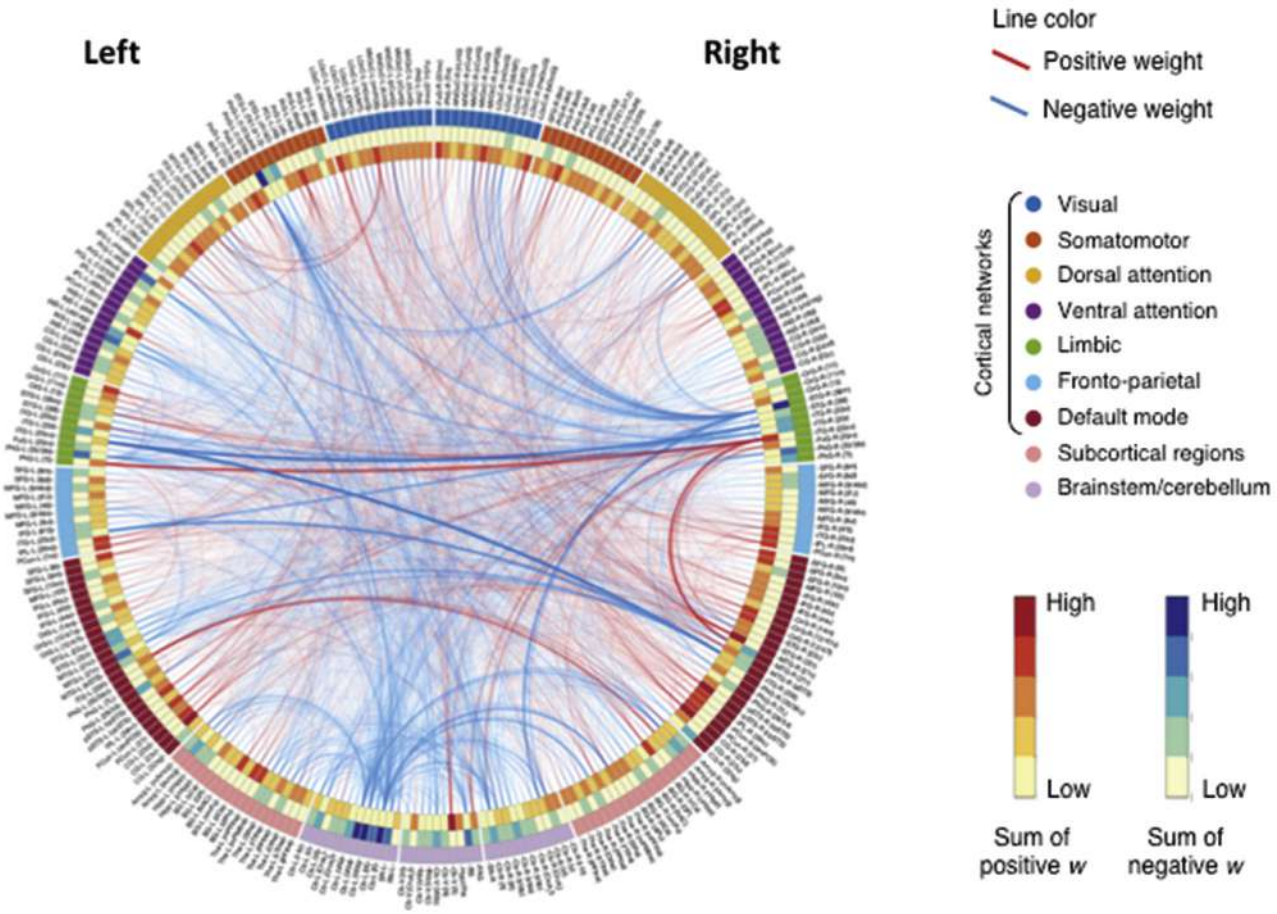
with radiolabeled water molecules (H_2O)[15] to measure changes in regional blood flow (rCBF) in response to pain.[89–91] However, PET was soon replaced by fMRI, which had better spatial and temporal resolution and did not require the injection of radioactive tracers. Subsequent PET studies capitalized on PET's unique ability to measure various neurochemical processes, notably opioid and dopamine receptor availability. Because the production of most of these tracers requires a cyclotron facility near the PET scanner, only a few sites in the world can conduct this type of research. Moreover, because the costs of PET imaging are high (approximately $1000–$3000 per scan depending on the tracer), sample sizes tend to be relatively low (often <20 participants). Consequently, PET appears to be a promising yet underutilized brain imaging technique.

The earliest PET studies of the opioidergic system employed selective μ-opioid radioligand [11C]carfentanil to measure changes in μ-receptor availability in response to tonic pain induced by the administration of topical capsaicin,[92] or injection of 5% hypertonic saline in the masseter muscle.[93] Both studies showed that pain induces the release of endogenous opioids in several brain regions, including the contralateral thalamus, amygdala, hypothalamus, Ins, ACC, and DLPFC. Interestingly, it seems that the degree of release of endogenous opioids by pain is inversely correlated with experienced pain,[93] suggesting that acute pain triggers the release of endogenous opioids, which in turn inhibits pain. Supporting evidence for this hypothesis came from a more recent PET-fMRI study showing that the release of endogenous opioids in the thalamus was associated with reduced BOLD activity in the same region.[94]

Early on, researchers also observed substantial interindividual variability in both μ-opioid receptor availability and in the activation of the μ-opioid system, which could in part be linked to different catechol-O-methyltransferase (COMT) gene polymorphisms.[95] COMT is an enzyme that metabolizes catecholamines and may indirectly affect opioid neurotransmission. Met/met carriers, who have lower COMT activity and higher pain sensitivity, display lower pain evoked μ-opioid activation in the thalamus, NAc, and pallidum, suggesting a lack of endogenous pain inhibition. PET could therefore help identify the cerebral mechanisms associated with genetic predispositions toward chronic pain in a way that may inform future therapeutic interventions.

A few studies have examined the state of the opioid system in various chronic pain disorders, such as arthritis,[96] central post-stroke pain,[97] and FM.[98] These studies have shown that chronic pain is associated with a decreased availability of opioid receptors in several brain regions involved in the perception and regulation of pain, such as the thalamus, amygdala, PAG, cingulate cortex, Ins, PFC, and parietal cortex (Fig. 10.8b). Moreover, in the study by Harris et al. on FM,[98] decreased receptor availability in the NAc was associated with increased pain ratings, a result that was replicated in a sample of patients with neuropathic pain.[99]

However, one recurring question with PET concerns the interpretability of binding potential: decreased receptor availability can either be because of a reduced number of receptors or to an increased level of endogenous neurotransmitters. To address this issue, Thompson et al. combined PET imaging with immunochemistry in a rat model of neuropathic pain and showed that decreased receptor availability is because of a reduced expression



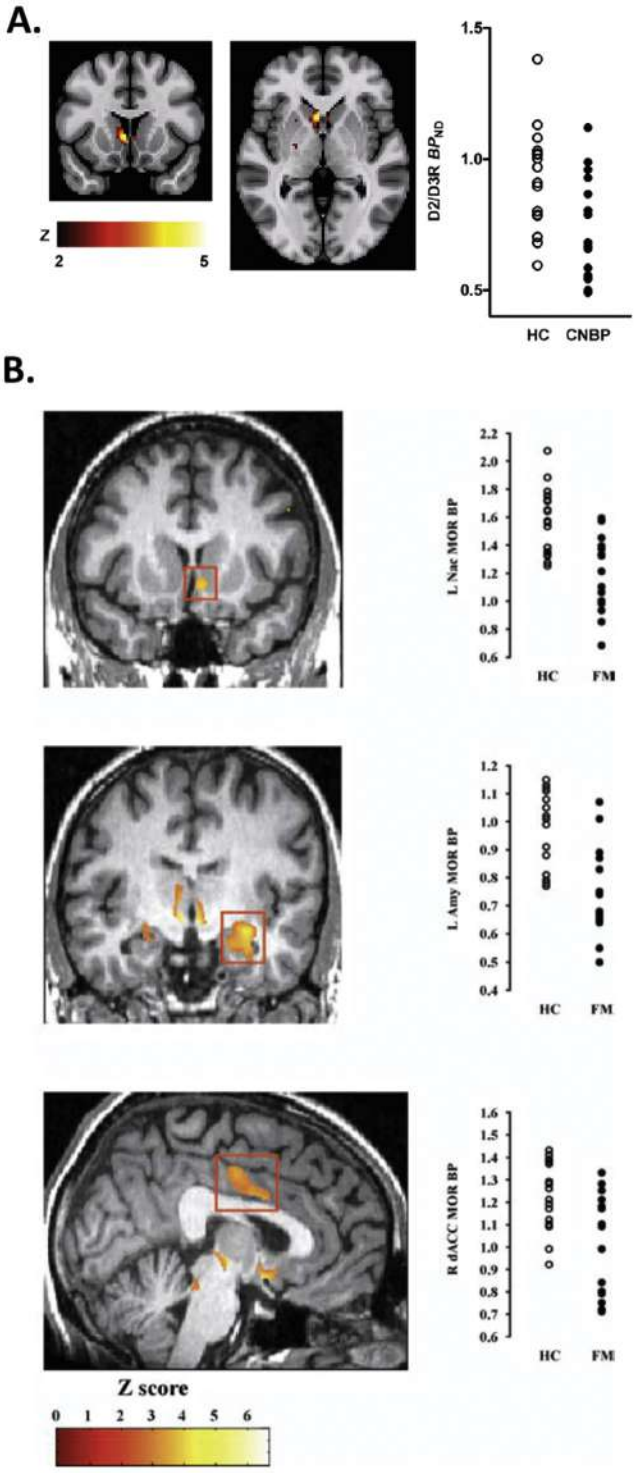
• **Figure 10.7** Tonic pain signature (ToPS). The pattern of functional connections that make the ToPS. The ToPS was trained to predict the pain produced by the oral administration of capsaicin and was found to be generalized to CLBP. The *outer circle* represents the different brain parcels used for the development of the ToPS as a function of the functional networks to which they belong (see the color code in the legend on the right). *Inner circles and lines* represent positive (warm colors) and negative (cold colors) connections, which significantly contribute to the ToPS. Lee JJ, Kim HJ, Čeko M. et al. A neuroimaging biomarker for sustained experimental and clinical pain. *Nat Med*. 2021;27:174–182. https://doi.org/10.1038/s41591-020-1142-7.[173]

of μ-opioid receptors.[100] Altogether, these results indicate that chronic pain is associated with reduced μ-receptor availability, which may compromise the brain's ability to regulate pain, and could explain the reduced efficacy of opioid therapy in many patients with chronic pain.

Several lines of evidence also suggest that dopaminergic system dysfunction may be associated with chronic pain. As mentioned above, genes involved in dopaminergic regulation seem to be predisposed to greater pain sensitivity.[101] Moreover, functional connectivity within the mesolimbic dopamine system (NAc-MPFC) has been repeatedly shown to be altered in patients with chronic pain.[58,51] PET studies using [11C]raclopride in healthy individuals have repeatedly shown that striatal D2/D3 receptor availability tends to be negatively correlated with pain sensitivity, suggesting that high synaptic endogenous dopamine tone might contribute to pain inhibition (but see [108] for contradictory findings).[102–105,106,107]

However, the relationship between dopamine receptor availability and chronic pain is more complex. Pain conditions that are primarily of neural origin, such as restless leg syndrome,[109] Parkinson's disease,[110] burning mouth syndrome,[111] and migraines in the ictal phase,[112] seem to be associated with an increased baseline availability of striatal dopamine D2/D3 receptors. In contrast, non-neurologic pain conditions, such as FM[107,108] and chronic back pain,[113] seem to be associated with a decreased baseline availability of striatal dopamine D2/D3 receptors, as well as a decreased pain induced dopamine response (Fig. 10.8a).[107,113] However, as for endogenous opioids, it is unknown whether decreased receptor availability in those conditions is related to increased dopamine release or reduced receptor density.

As mentioned previously, another important question concerns whether differences between patients and controls reflect stable traits predisposing people toward chronic pain or consequences of being in pain. While increased receptor availability in neurological disorders such as burning mouth or restless leg syndrome seems to contribute to the etiology of the condition, it is probable that reduced receptor availability in musculoskeletal disorders such as CLBP reflects the consequences of prolonged pain. One interesting possibility could be that dopaminergic dysfunction in these chronic pain syndromes is related to a general "illness response" whereby sustained pain causes systemic inflammation, which in turn reduces dopaminergic signaling to promote rest and recovery.[115] This could explain the gradual appearance of the different comorbidities that often accompany chronic pain: widespread pain, fatigue, cognitive deficits, anhedonia, and depression.[114]



• **Figure 10.8** Positron emission tomography (PET) studies of chronic pain. A, Levels of striatal D2/D3 receptor binding potential (BP_{ND}) in chronic non-neuropathic (CNBP) patients and healthy controls (HC). Significant reductions in D2/D3 receptor BP_{ND} compared with HC samples were observed in the right ventral striatum. Adapted from Martikainen, et al. (2015).[113] B, Levels of the μ-opioid receptor (MOR) binding potential (BP) in chronic non-neuropathic (CNBP) patients and HC. Significant reductions in MOR BP compared with HC sample were observed in the left ventral striatum (*top*), left amygdala (*middle*), and right dorsal anterior cingulate cortex (dACC; *bottom*). Note that images are displayed in radiological convention where the left hemisphere is shown on the right side of the image. Adapted from Harris et al.

While the exact sequence of events remains to be determined, the recent development of certain markers of glial activation, which bind to the translocator protein (TSPO), has allowed to observe increased glial activation in the thalamus and somatosensory cortex of patients with CLBP.[115] Moreover, TSPO expression in the ACC/PFC and Ins has been shown to correlate with depressive symptoms associated with chronic pain.[116,117] Finally, a recent multi-site study of patients with FM fibromyalgia also showed increased TSPO expression in the parietal, somatosensory, and motor cortices. Despite the several caveats associated with TSPO imaging,[119] these results indicate that neuroinflammation may be associated with certain pain states such as CLBP or FM.

Electroencephalography

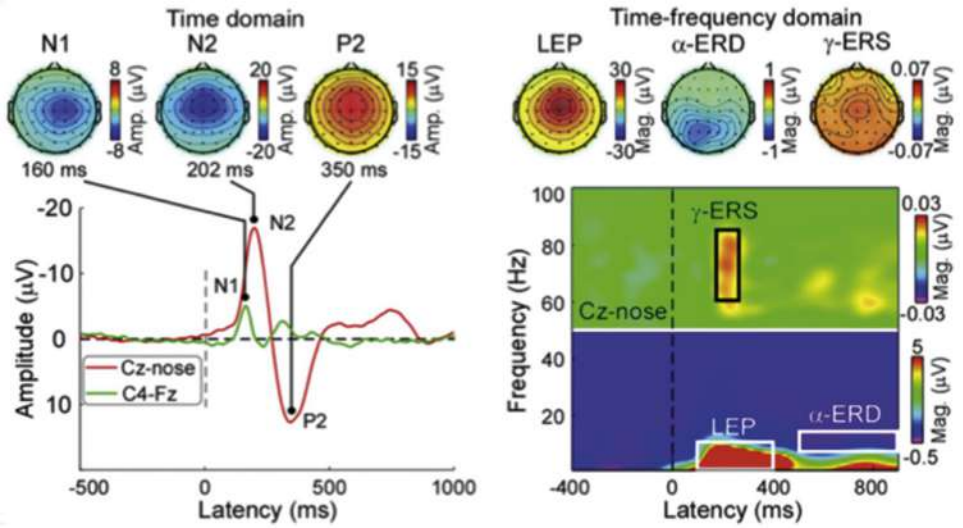
Electroencephalography (EEG)[119] and magnetoencephalography (MEG)[120] are direct and non-invasive measures of brain function. While EEG measures the small electrical currents resulting from postsynaptic potentials, MEG measures the magnetic fields induced by these currents. The major strength of both methods is their high temporal resolution in the range of milliseconds. Thus EEG and MEG perfectly complement fMRI, which has an excellent spatial but lower temporal resolution. A particular strength of EEG is that it is cost-effective, broadly available, and mobile. Thus EEG lends itself to broad clinical use. The limitations of EEG are its low spatial resolution and insensitivity to processes in deep brain areas. As magnetic fields are not distorted by the scalp and skull, MEG has a higher spatial resolution than EEG. The downside of MEG is that it is technically more demanding, more expensive, rarely available, and stationary. However, novel sensor types of MEG might render it more cost effective and mobile in the future.[121] In the following sections, we will use the term "EEG" for convenience, but most parts apply similarly to MEG.

EEG Measures of Acute Experimental Pain

The most popular EEG approach to pain is the assessment of evoked potentials in response to brief noxious stimuli, such as thermal laser stimuli of milliseconds duration.[122] This approach yields a typical sequence of responses that are termed N1, N2, and P2,[122] based on their sequence and polarity (Fig. 10.9). Source localization of EEG recordings and intracranial recordings have shown that these responses originate from core areas of the brain network associated with pain processing, that is, from S1, the operculo-insular region, the aINS, and the cingulate cortex.[123,124] The analysis of evoked potentials yields two main readouts: the latencies and amplitudes of the different responses.

The amplitudes of evoked potentials have been shown to vary with objective stimulus intensity and subjective perception of pain under many different experimental conditions.[125] However, innovative paradigms have revealed that the relationship between evoked potential amplitudes and pain is not one-to-one.[126] Instead, evoked potentials are currently thought to reflect the importance[127] of noxious stimuli and defensive actions rather than pain.[128] Thus the initial hope that evoked potentials represent a reliable biomarker of pain has not been answered. Evoked potentials are sensitive to damage to nociceptive pathways. Thus they have been established as a clinically useful measure of the integrity of nociceptive pathways in the brain.[129,130]

Time-frequency analyses complemented and extended the evoked potential approach. These analyses have revealed that brief noxious stimuli modulate neuronal oscillations at α (8-13 Hz), β (13-30 Hz), and γ (40-100 Hz) frequencies (Fig. 10.9) that partially



• **Figure 10.9** EEG Measures of acute experimental pain. *Left*, Time-domain analyses of EEG data show the temporal sequence of evoked potentials in response to painful stimuli, including N1, N2, and P2. *Right*, time-frequency analyses of M/EEG data show induced responses at α (a-ERD) and γ (g-ERS) frequencies in response to painful stimuli. Adapted from Hu & Iannetti.[174]

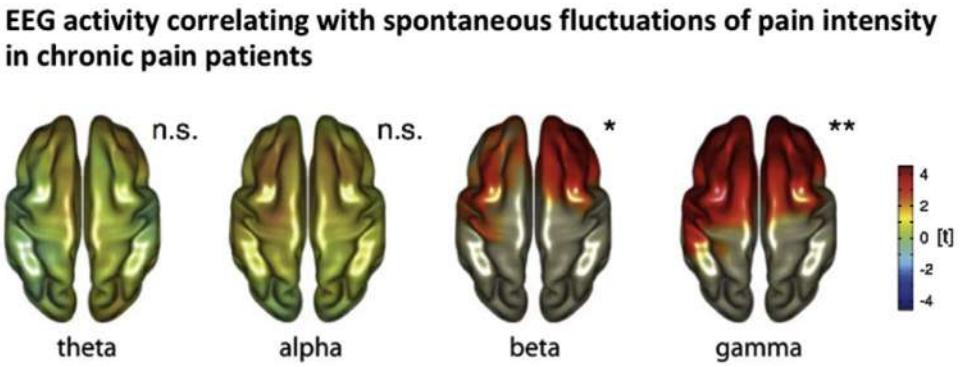
overlap in time and space with the evoked potentials.[131–133] In particular, γ oscillations originating from S1 are closely related to the subjective experience of pain.[134] This close relationship has been observed during spontaneous variations of pain as well as during experimental manipulation of pain in animals and humans.[133,135,136] Recent optogenetic inductions of γ oscillations in mice have demonstrated that they are indeed casually related to pain.[137] It has been shown that γ oscillations in the S1 yield network effects in the PFC and subcortical brain areas. Thus γ oscillations are the EEG responses most closely related to pain. However, this relationship is not one-to-one. For instance, during placebo manipulations, the dissociation of γ oscillations and pain has been found.[138] This dissociation might reflect that γ oscillations could be more closely related to behavioral responses to noxious stimuli than their perception.[139] Thus similar to the lack of a certain brain area encoding pain, no single brain response determines pain at a certain latency or frequency. Instead, pain is most likely encoded by complex patterns of brain activity, which include not only neuronal activity in different brain areas but also brain activity at different latencies and frequencies.

Finally, novel paradigms of experimental pain have extended the EEG-based assessment of pain from brief noxious stimuli to longer-lasting tonic stimuli as a first step toward the main clinical problem of ongoing pain.[140–144] The results showed that tonic pain is associated with decreases and increases in brain activity at α and γ frequencies, encoding objective stimulus intensity and subjective pain intensity, respectively. Moreover, the patterns of brain activity during tonic noxious stimulation fundamentally differ from those of brief noxious stimuli, with a shift from the encoding of pain intensity by activity in multiple frequency bands in somatosensory cortices to an encoding by γ oscillations in the PFC.[140,141,143] This again highlights the important role of γ oscillations in the brain processing of pain. Moreover, it shows that insights into the brain mechanisms of brief experimental pain cannot easily be transferred to longer-lasting pain, including chronic pain states.

EEG Measures of Chronic Pain

Although EEG is available in nearly every neurology office and department, evidence on the EEG correlates of chronic pain is surprisingly limited.[145,146] To date, two different EEG approaches have been investigated. The first uses the evoked potential approach to investigate whether the processing of painful or non-painful stimuli is abnormal in chronic pain. The results show that damage to nociceptive pathways in neuropathic pain is associated with a reduction in evoked potentials.[130,146] Other abnormalities such as a disinhibition or lack of habituation of evoked potentials in some chronic pain conditions such as migraine or FM are not consistently found.[146] Moreover, it remains unclear how these findings relate to the basic pathology of chronic pain and phenomena such as central sensitization.[147]

The second approach quantifies ongoing EEG activity during the resting state in patients with chronic pain. The earliest finding was a slowing of α activity and a widespread increase in brain activity at θ frequencies (3-8 Hz).[148,149] Together with evidence from thalamic recordings,[150,151] these observations have motivated the thalamocortical dysrhythmia model of chronic pain.[152] In this model, abnormal nociceptive input yields abnormal thalamic bursts at θ frequencies. These θ oscillations are transmitted to the cerebral cortex, which results in disinhibition of neighboring areas, which in turn results in abnormal oscillations at γ frequencies and eventually in ongoing pain. This model is highly appealing, but the evidence is inconsistent. While some studies in animals provided further support for the model,[153,154] other EEG studies in larger cohorts of patients did not find abnormal θ activity.[155,156] However, a recent resting state EEG study in a large cohort of patients indicated that patients with chronic pain had higher prefrontal γ oscillations and global network reorganization at γ frequencies.[156] Other EEG studies have shown further changes in brain oscillations and connectivity within and across intrinsic brain networks at θ, α, β, and γ frequencies in patients suffering from different types of chronic pain.[157,158] Thus accumulating evidence implicates complex changes in brain network function, particularly oscillations and connectivity at γ frequencies in the brain mechanisms of chronic pain. This is further supported by the recent observation that the momentary intensity of chronic pain was positively related to γ oscillations in the PFC (Fig. 10.10).[159] However, owing to their low signal-to-noise ratio and sensitivity to artifacts from muscles, the assessment of pain-related gamma oscillations using EEG remains challenging.



• **Figure 10.10** EEG Measures of chronic pain. Topographies of the correlation of neural oscillations with spontaneous fluctuations of pain intensity in patients with chronic back pain. Neural oscillations over the prefrontal cortex at β and γ frequencies are significantly related to pain intensity. (May et al.)[160]

Other recent studies did not directly address the EEG correlates of chronic pain, but investigated whether EEG signals can predict an individual's response to analgesic treatment and/or sensitivity to pain. First, results have revealed that some EEG features, such as the amplitude of delta (1-3 Hz) activity during tonic pain, can predict treatment success (e.g. the responsivity to post-surgical opioid treatment).[160–162] Other studies have indicated that the individual peak frequency of sensorimotor α oscillations relates to an individual's sensitivity to experimental pain.[163,164] In particular, the lower the peak α frequency, the higher is the sensitivity to pain. As sensitivity to pain represents an important predictor of chronic pain, the analysis of α oscillations and their peak frequency represents an appealing and clinically useful direction for future studies.

EEG for Clinicians: Current State and Future Perspectives

EEG using the evoked potential approach is the first clinically useful measure of pain-related brain activity. The approach objectifies damage to nociceptive pathways, thereby helping to establish a diagnosis of neuropathic pain. Consequently, it has been included in the guidelines for the assessment of neuropathic pain.[130] While other EEG measures are not yet ready for clinical use, the first steps have been made toward the development of clinically useful biomarkers of pain.[165] Such biomarkers could be diagnostically useful when verbal reports are not available or reliable. Moreover, they could help predict and classify chronic pain and tailor individual treatment. In addition, EEG-based biomarkers of chronic pain could represent direct targets of pain therapy. For instance, abnormal EEG patterns might be modulated by neurofeedback,[166] non-invasive brain stimulation,[167] or sensory entrainment approaches,[168] which can selectively alter neuronal oscillations at certain frequencies. As EEG is broadly available, potentially portable, and can easily be used in medical offices or at home, an EEG-based biomarker of pain is particularly appealing. The integration of EEG-based information with other measures resulting in multimodal composite biomarkers of pain might further enhance the clinical usefulness of such biomarkers.[169]

Conclusion and Future Directions

The subjective experience of pain is a product of brain activity. Therefore any biologic explanation of pain will have to ultimately explain how it is generated by the brain. Intuitively, it seems that nociceptive signals coming from the periphery should ultimately reach a "pain center" in the brain where the subjective experience of pain is generated. However, decades of brain imaging research suggest that there is no one-to-one relationship between pain and any pattern of brain activity. Unlike other senses, there does not seem to be a brain region or set of brain regions specifically dedicated to pain processing.[34] Rather, pain seems to be encoded by distributed fine-grained patterns of brain activity spanning several brain areas. In that respect, the cerebral representation of pain might be more similar to that of emotions.[33] Indeed, the concept of pain appears to regroup various sensations designed to have a protective function. Recent advances in machine learning have allowed the development of multivariate pain neurosignatures,[27,170] that can reliably predict pain based on brain activity. However, these neurosignatures should not be interpreted as unique and inflexible pain-predictive patterns. They are quite the contrary: neurosignatures represent vast multivariate patterns within which various, and sometimes even quite distinct, patterns of brain activity can equally represent pain. Altogether, recent advances in fMRI research indicate that there is degeneracy in the relationship between brain activity and pain perception, whereby a diversity of brain activity patterns can equally represent pain within the soft constraints of a few neurosignature patterns, the number of which remains to be determined.

Moreover, several studies have demonstrated that the development of MRI-based biomarkers for various chronic pain conditions is now feasible.[23] Biomarkers can be used for diagnosis, prognosis, prediction of treatment outcomes, and precision medicine as surrogate endpoints to monitor the evolution of the condition or to track treatment efficacy.[23] However, prediction accuracies are still insufficient for practical purposes, and their specificity and generalizability remain uncertain. The main obstacle for the development of chronic pain biomarkers is the current lack of large datasets of patients. For instance, the UK biobank currently comprises close to 15 000 participants reporting chronic pain with brain scans (https://www.ukbiobank.ac.uk/). However, phenotyping is minimal. Researchers can also access existing datasets on openpain.org, an open registry of brain imaging studies. Collectively, these different resources should greatly improve our capacity to develop brain-based biomarkers for chronic pain.

Therefore brain imaging of chronic pain will likely follow the path laid out by other neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia, or depression, in identifying brain markers of disease.[22] However, it is still unclear whether chronic pain constitutes a brain disease in the same sense as these other neuropsychiatric disorders, which could lead the field to face challenges unique to chronic pain. Pain is a subjective experience

generated by the brain. Therefore any biologic explanation for it will inevitably stumble upon the complexities associated with the question of mind-body relationships. Moreover, chronic pain syndromes constitute a heterogeneous category of multisymptomatic disorders, for which pain might not always be the most important or central feature. Therefore it is unclear whether brain imaging can differentiate between different clinical phenotypes or whether it should be attempted to accomplish this. There may be more value in identifying different brain imaging phenotypes rather than simply confirming clinical phenotypes. Indeed, if the principle of degeneracy also applies to chronic pain conditions, then this would mean that different brain phenotypes could underlie the same clinical phenotype, and consequently, different subgroups of patients may benefit from different types of treatment.

Different brain imaging techniques are highly complementary and may serve different purposes. For instance, EEG might prove quite sensitive and easy to administer, but its specificity might be an issue. Therefore it could be well suited to serve as a first screening tool.[171] RsfMRI may be more specific, but the neurophysiologic mechanisms underlying functional networks remain opaque, making it difficult to use rsfMRI to identify new targets for treatment. Multimodal MRI techniques examining different aspects of brain structure (e.g. gray matter density, cortical thickness, subcortical structure volume, diffusion, tractography, perfusion, magnetization transfer, MR spectroscopy) appear to convey information that could eventually be used for developing new therapeutic targets. However, there is a large gap between the indirect indices of brain macrostructure obtained with MRI and the underlying cytoarchitectural processes that could potentially be used as targets for treatments. One potentially promising and currently underexplored avenue for future research could be to combine human and rodent brain imaging to identify the cytoarchitectural changes associated with pain-related plasticity in homologous brain regions. PET may provide more direct information about potential treatments, but high costs and reduced access to facilities capable of producing specific radioligands remain an important limitation. Finally, one exciting recent development has been the creation of pain-predictive neurosignatures, which currently do not have the sensitivity or specificity to be used as clinical tools but could be improved to potentially make clinically relevant predictions.

Overall, the practical contribution of brain imaging to clinical practice remains difficult to assess beyond basic investigations of CNS damage. However, brain imaging techniques have clearly contributed to changing our concept of pain from a symptom of objective tissue damage to that of a subjective experience generated by the brain. In this sense, brain imaging has broadened the historical focus of pain research and treatment of peripheral and spinal mechanisms toward a concept that now embraces peripheral, spinal, and cerebral mechanisms equally.

Key Points

- Early brain imaging research identified a collection of brain regions associated with evoked pain, often referred to as the "pain matrix" (thalamus, ACC, Ins, S1, S2). However, the activity of these structures appears to be relatively unspecific to pain.
- Recent developments in machine learning have allowed the development of more specific multivariate pain-predictive neurosignatures that use fine-grained patterns of brain activity to predict evoked pain.
- The relationship between brain activity and experience pain appears to be characterized by degeneracy, meaning that there is a many-to-one relationship between patterns of brain activity and pain.
- The patterns of activity associated with chronic pain appear to be qualitatively different from those associated with evoked pain.
- Findings from brain imaging research could potentially explain the dissociation between nociception and self-reported pain observed in certain chronic pain syndromes.
- Brain imaging findings of patients with chronic pain can reflect at least three different aspects of chronic pain: (1) stable traits that precede the onset of the painful condition and that confer vulnerability toward pain chronicity, (2) the chronic pain "state," which gradually develops as pain becomes chronic and remains prolonged in time, and (3) ongoing pain, which can fluctuate more rapidly in the range of minutes or hours.
- Provided sufficient data, pain-predictive biomarkers could be developed to make clinically relevant predictions.
- Using EEG for the development of a biomarker of pain is appealing as it is broadly available, cost effective, and potentially mobile. This approach is under development but is not yet ready for clinical use.

Suggested Readings

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11

Individual Differences in Experience and Treatment of Pain: Race, Ethnicity, and Sex

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Though the experience of pain is nearly universal, the experience and burden of pain vary across race, ethnicity, sex, and gender. This chapter will discuss the disparities in the experience and burden of pain and variability in responses to treatment across these groups.

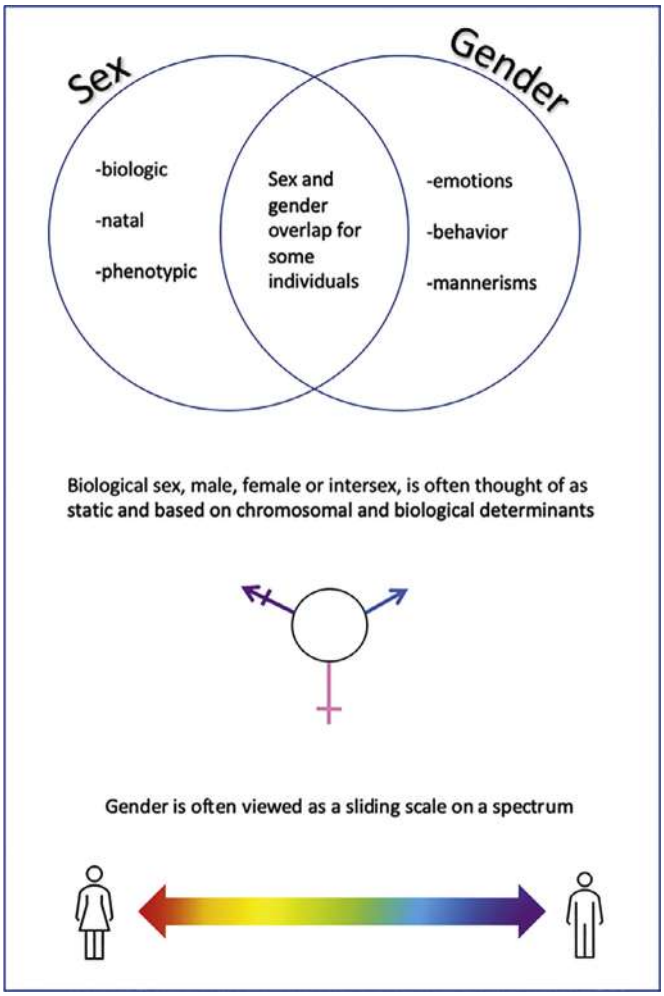
Clarification of Terminology

Race and ethnicity are often used interchangeably in both colloquial language and research. However, these represent two different constructs. Race refers to groups with common descent or heredity, shared physical characteristics, culture, and self-identity [e.g. non-Hispanic White/Caucasian, Black/African American, Asian, Native American/Native Canadian], whereas ethnicity indicates cultural groupings with a common language, religion, nationality, or heritage (e.g. Hispanic/Latinx).[1,2] In this chapter, we will use the term non-Hispanic White (NHW) to refer to anyone of White or Caucasian descent, African American (AA) to refer to anyone of Black or African descent, and Hispanic to refer to anyone of Hispanic descent or who identifies as Latinx. Similarly, sex and gender are not interchangeable. Sex is defined as the biologic phenotype an individual is born with that can be categorized as either male, female, or intersex, while gender is an individual's expression of internal identification that may fall into preexisting social, behavioral norms. Gender consists of a set of cultural behaviors that society has assigned to a specific sex (e.g. cooking is considered a task for women while plumbing is a task for men); thus gender is a social construct. Gender is also viewed on a spectrum between male and female and can evolve throughout one's lifetime. An individual's sex and gender are not always synchronous; therefore an individual may have a natal sex that does not correspond with their expressed gender (see Fig. 11.1). In the current chapter, we will be addressing the influence of race, ethnicity, and sex on the experience, burden, and treatment of pain.

Racial and Ethnic Differences in Pain

Racial and ethnic differences in the pain experience are consistently demonstrated across experimental and laboratory-based studies. In the United States, much of this literature has focused on AA/NHW differences, and the results are not always consistent. In general, research has demonstrated that, compared to NHW individuals, AA individuals are more sensitive to nociceptive stimulation (i.e. lower thresholds) and less tolerant of pain overall,[3] though these results have some variability based on the modalities and outcomes assessed. Groups of NHW individuals demonstrate, on average, a higher cold pain tolerance and provide lower pain ratings (i.e. thresholds) for cold-induced pain than do groups of AA individuals.[3] Although there are not AA-NHW differences in heat-induced pain thresholds, NHW people show a higher heat-induced pain tolerance and provide lower suprathreshold heat pain ratings than AA people.[3] Regarding pressure pain, AAs have lower pressure pain thresholds than NHWs.[4] AAs also have a lower tolerance to ischemic pain than NHWs, though there are no differences in ischemic pain threshold.[2,5] AA participants in experimental pain studies also rate mechanical pricking pain as more intense than do NHW participants in such studies.[6] In addition to these pain sensitivity measures, there are also AA-NHW differences in experimental measures of centralized pain facilitation and inhibitory pain modulation (i.e. temporal summation and conditioned pain modulation [CPM]). AA individuals demonstrate consistently higher temporal summation of pain than NHWs.[6] However, the CPM literature is small and inconclusive; one study found that AAs showed less CPM than NHWs,[5] but other studies found no racial/ethnic differences in CPM.[6]

Although much of the disparities literature has focused on differences between AA and NHW individuals, there is some recent evidence of disparities in experimental pain sensitivity among Hispanics, Native Americans (NAs), and Asians. Asians consistently demonstrate a lower tolerance and higher suprathreshold cold pain ratings relative to comparison groups such as NHW.[7] Hispanics also demonstrate lower pain tolerance and provide greater suprathreshold pain ratings relative to NHWs.[8] Asian and Hispanic people also report lower threshold and tolerance for heat pain.[8,9] However, Asians have a higher pressure pain threshold than AAs.[10] Few studies have compared experimental pain processing between NAs and other groups. Such studies have indicated that AAs reported higher electric pain thresholds and lower pain ratings than NHWs.[11] There were no differences in temporal summation between NA and NHWs.[11] Collectively, the literature on laboratory-based pain assessment suggests that individuals from racial and ethnic minority backgrounds (many of whom have likely experienced substantial discrimination and mistreatment) appears to suggest an overall



• **Figure 11.1** Sex and Gender Infographic. Sex is viewed as a fixed biological trait while gender is an individual's expression.

increase in pain sensitivity among individuals from these minority groups relative to individuals reporting their ethnic/racial background as "White."

Besides racial and ethnic disparities in experimental and laboratory-based pain, there are also considerable differences in the experience of clinical pain conditions. For example, osteoarthritis (OA) is an increasingly common painful musculoskeletal condition. While AAs show a greater likelihood to have both radiographically confirmed and symptomatic OA,[12] NHWs have a higher age-adjusted prevalence of chronic pain overall than do AAs.[13] This difference was negated when the researchers only considered high impact chronic pain (i.e. chronic pain that frequently limits life or work activities).[13] Other studies show quite a different pattern. Numerous studies demonstrated that AAs and other minority groups report more severe acute and chronic pain.[2,6] Compared to NHWs, AAs report more pain from chronic conditions such as AIDS[14] and glaucoma,[15] greater postoperative pain,[16] more pain sites and greater pain severity, depression, and disability, and have poorer outcomes on performance testing that is sensitive to the functional impact of chronic pain (e.g. timed-up-and-go task, 6 min walking test).[2,17,18] Disparities in clinical pain exist between NHW and other minority groups as well. For example, minority patients report more severe low back pain than do NHWs.[19] While Hispanic individuals report fewer pain conditions and experience less pain interference than NHWs, they have more severe clinical pain,[20] Hispanic individuals also report greater postoperative pain.[16] Although studied to a lesser degree, Asians also report greater pain intensity than do NHWs, particularly for knee OA.[21] NAs are also more likely to experience pain complaints than the general United States population.[22,23] Overall, the literature on acute and chronic clinical pain indicates that the experience and adverse impact of pain may be more frequent and severe in groups of individuals from non-White racial and ethnic backgrounds.

Sex and Gender Differences in Pain

Beyond race and ethnicity, the perception and experience of pain also vary as a function of sex. In laboratory settings, women demonstrate lower pain thresholds and tolerance and provide higher pain ratings for mechanical-, electrical-, thermal- (both heat and cold), and chemical-induced nociceptive stimulation than men.[24,25] In addition to these measures of general pain sensitivity, women also exhibit greater central pain facilitation (e.g. temporal summation of pain) and less effective endogenous inhibitory control of pain (e.g. CPM).[26,27] Moreover, women demonstrate a lower threshold for eliciting the nociceptive reflex, an involuntary spinal reflex resulting from electrical nerve stimulation.[28]

Similar sex differences are found for clinical pain. Indeed, large epidemiologic studies across geographic regions indicate that pain is more frequently reported by women than men,[25] women are more likely to seek treatment for pain, and that women consistently report higher pain ratings than men across diagnostic groups.[29] There is a higher prevalence of numerous painful diseases among women. Women are nearly twice as likely to experience neuropathic pain than men.[30] They are also more likely to experience musculoskeletal (MSK) pain and report greater pain severity among MSK conditions[31], across 17 countries and six continents, women had a higher prevalence of MSK pain (45%) than men (31%).[32] This is specifically true for fibromyalgia, back pain, and osteoarthritis-related pain.[33,34] Women are also more likely to report pain across ten different anatomical regions and chronic widespread pain.[35] They are also at higher risk of experiencing abdominal pain such as interstitial cystitis.[36] In fact, there is a 3:1 female-to-male ratio of irritable bowel syndrome (IBS) prevalence.[37] Regarding headaches, women are more likely to experience tension-type headaches and migraines.[36,38] These sex disparities are also prominent in post-procedural pain. Women not only experience greater acute pain following various procedures, including cholecystectomy, hernia repair, colonoscopy, general outpatient surgery, and orthopedic surgeries,[39] but also greater chronic postsurgical pain following total knee arthroplasty (TKA).[40] However, there are no sex differences in chronic postsurgical pain following total hip arthroplasty, gallbladder surgery, or hernia repair.[41–43] There is also no consistent evidence for sex differences in cancer pain.[25] Thus there appear to be discrepancies in sex differences depending on the nature of the pain and treatments received.

Racial and Ethnic Differences in Pain Treatments Provided

It is well documented that racial and ethnic minorities have disproportionately more unrelieved pain than NHWs. This is because of racial and ethnic differences in both the assessment administered

and treatments prescribed for pain across various conditions and settings.

Traditionally, racial and ethnic minorities and other vulnerable groups (e.g. homeless) are more likely to seek and receive care in the emergency department (ED).[44] However, the care they receive in the ED is not equivalent to that received by NHWs. The ED care delivered to individuals from racial and ethnic minority backgrounds is of consistently lower quality, as outlined below. For example, minority groups have longer wait times and are less likely to be admitted as inpatients than NHWs.[45] Minority patients also wait longer to receive pain medications in the ED than do NHWs.[46] Results of a recent meta-analysis including 13 studies of racial disparities in pain care in United States EDs found that AAs were 36% less likely, Hispanics 30% less likely, and Asians 42% less likely to receive analgesics than NHW patients with similar injuries and complaints. Similarly, AAs were 35% less likely and Hispanics 23% less likely than NHWs to receive opioids for acute pain.[47] Moreover, NHWs are 82% more likely than AAs to be discharged with a prescription for analgesics and 98% more likely to be discharged with an opioid prescription.[48] In fact, AAs are less likely to receive opioid prescriptions in the ED than any other group racial or ethnic group.[49] Perhaps this is because providers are more likely to view AA patients as drug-seeking. Indeed, although ED staff perceive only 7%-9% of the general patient population to be opioid dependent, they believe that opioid dependence affects a substantially higher percentage, 13%-17%, of patients with sickle cell disease, a disease that primarily affects AA individuals.[50] Moreover, 22% of ED physicians believe that more than half of patients with sickle cell disease are addicted to opioids despite only 2%-4% actually meeting the criteria for a substance use disorder.[51,52]

Across other treatment settings, AA individuals are twice as likely as other racial and ethnic groups to have their pain underestimated by the physicians.[53] Minority patients are also less likely to be treated in pain clinics and receive comprehensive diagnostic and treatment for pain than NHWs.[54] When minority patients are treated, they receive lower doses of analgesic medications,[55] are less likely to receive opioids, and are less likely to undergo surgical procedures (e.g. joint replacement)[49,56,57] despite having a higher prevalence of painful conditions and reporting higher pain scores.[58]

Sex Differences in Pain Treatment

Much like racial and ethnic minorities, women are at greater risk for the undertreatment of pain. They often receive less treatment, and the treatment they receive is less effective at providing pain relief.[25] In one study in the ED, women were less likely to be prescribed opioid medication than men.[58] Likewise, Hamberg and colleagues found that women with neck pain were more likely to receive non-specific somatic diagnoses and analgesic and psychoactive medication prescriptions, regardless of the sex of the provider.[59] Other studies have found that pain treatment differs because of the interaction between patient and provider sex. In one study, female providers prescribed higher opioid doses for women than men with low back pain, whereas male providers prescribed higher doses for male patients.[60] Another found that female providers were more likely to recommend psychosocial treatments (i.e. anti-depressants and mental health referrals) for female than male pain patients.[25,61] This is consistent with evidence suggesting that women may be more likely to be mistrusted and "psychologized" by their providers, regardless of the sex of the provider.[62] Unfortunately, this only increases distress among female patients that then may contribute to a cycle of chronic pain. While relatively little research has examined the intersectionality of race and sex related to chronic pain, it appears likely that AA women may be at particular risk for undertreatment and for having their pain reports underestimated or dismissed.[63]

Racial and Ethnic Differences in Pain Treatment Outcomes

Beyond disparities in how pain is treated, there are also disparities in treatment outcomes when treatments are provided. Pain interventions (both pharmacologic and nonpharmacologic) may cause disparate analgesic effects based on race, ethnicity, and sex. For example, compared to NHW individuals, AA individuals are not only less likely to opt for surgical treatment options such as a total joint replacement,[64] but when AA individuals do receive treatment (e.g. hip and knee arthroplasty, spinal surgery), they also report greater pain intensity, pain-related disability, and pain frequency than NHW individuals.[65] A retrospective study using data from the Spine Patient Outcomes Research Trial found that of patients with spine disorders those that underwent spinal surgery had an improved outcome compared to those in the nonoperative treatment group.[66] However, of those in the surgical group, the NHW patients reported significantly greater improvement in pain outcomes than the AA patients.

The effect of race and ethnicity on surgical treatment outcomes are subject to the intersectionality of socioeconomic factors. Indeed, Goodman et al.[65] used self-reported and census data to investigate the interaction between race and socioeconomic variables on the outcomes of TKA. They found that worse pain outcomes were associated with race and socioeconomic factors and that AA patients from poorer communities showed evidence of suffering from a double disparity.

The research on racial disparities in nonsurgical pain treatment outcomes is scant and shows mixed results. In a laboratory study of opioid analgesia, researchers found that AA participants showed a greater analgesic response to morphine and butorphanol than NHWs.[67] Concerning multi-disciplinary pain treatment outcomes, evidence suggests no racial or ethnic differences in treatment efficacy, including a reduction in pain severity. For example, Cano et al. demonstrated that controlling for age, sex, and other social determinants of health still resulted in a lack of racial and ethnic differences.[68] In contrast, Merry and colleagues[69] found that NHW and AA patients experienced improvements in pain-related interference following multi-disciplinary pain treatment, but only NHW participants reported reduced pain severity. A study of a cognitive-behavioral self-management program for chronic back pain showed yet a different pattern of results. While NHW, AA, and Hispanic participants all showed improvements in disability, only Hispanic participants improved in pain intensity.[70] Taken together, it is clear that racial and ethnic minority patients experience different outcomes from treatment than NHWs. However, the evidence does not provide a consistent pattern of disparities.

Sex Differences in Pain Treatment Outcomes

The literature, including several meta-analyses, describes sex differences in pain treatment outcomes, especially for opioid analgesia. One such review found that women have a lower opioid

consumption post-surgically than do men.[71] A meta-analytic review of 11 studies found that women not only self-administer lower daily doses of opioids via patient-controlled analgesia pump (PCA) but also receive lower daily doses of opioids for chronic non-cancer pain.[72] Moreover, women experience greater morphine-induced analgesia than do men across experimental and clinical studies.[73] Together, this suggests that women respond better to opioids and require lower amounts than men for both acute and chronic pain. However, it is important to note that women are also more likely to experience opioid-induced side effects and mortality than men,[74,75] which may result from their increased sensitivity to the effects of opioids.

Sex differences in response to surgical pain treatment are consistent. Overall, women fare worse than men across surgical types and outcomes. Among patients undergoing orthopedic surgery, women reported a greater "worse pain" intensity since surgery and more time spent in severe pain than did men.[76] Similarly, women are more likely than men to have persistent post-surgical pain three months following orthopedic trauma surgery.[77] Women also report higher pain than men following rotator cuff repair. However, these differences dissolve after one year.[78] It is important to note that while others have also acknowledged sex differences in pain, disability, and quality of life following orthopedic surgery, with women experiencing worse outcomes than men, women consistently had greater pain, disability, and poorer quality of life pre-surgically. After controlling for baseline differences, there were no sex differences in symptom improvement.[79] Thus it is important to identify presurgical factors that may differ between men and women that may be contributing to sex differences in post-surgical pain.

There is also evidence of sex differences in outcomes for non-pharmacologic pain interventions, although these results are more inconsistent. For example, response to inter-disciplinary pain management programs may differ by sex. Keogh and colleagues found that although inter-disciplinary pain management was effective at reducing pain for both men and women, men reported ongoing relief after three months, whereas women's pain had returned.[80] In other studies, however, women showed greater improvement than men in pain and pain-related disability following a multimodal pain management program.[81] Thus sex differences in outcomes of multimodal treatment may depend on the specific outcome (pain severity vs. disability) and the timing of follow-up. However, it is important to note that across studies of these inter-disciplinary, multimodal pain treatment programs, most patients are female. Thus more research may be needed to better understand the effectiveness of such programs among men. Regarding other non-pharmacologic treatments such as physical therapy, conventional physical therapy (e.g. heat, cold, massage, stretching, electrotherapy, and exercise) has shown to be more effective for men while intensive dynamic exercises are more effective for women.[82] There is also some evidence that women are more responsive to psychological pain interventions. For example, women undergoing cognitive-behavioral therapy showed improved quality of life, whereas men did not.[83] Likewise, there is evidence that acceptance-based interventions for pain may be more helpful in reducing pain for women than men.[80] Sex differences in the pain experience (e.g. coping, catastrophizing, negative affect) may explain some of these treatment differences. Specifically, psychological interventions often target pain mechanisms such as catastrophizing. Perhaps the changes in these constructs as a result of treatment vary by sex, thus resulting in more broad sex differences in treatment outcomes.

Contributing Factors to Racial, Ethnic, and Sex Disparities

Coping

Pain coping refers to the thoughts and behaviors people use to manage their pain or their emotional reactions to their pain.[84] Coping strategies are differentially associated with pain-related outcomes. Active coping, an attempt to control pain or function despite pain, includes strategies such as coping self-statements, diverting attention, exercise, and ignoring the pain. In contrast, passive coping is an attempt to relinquish control of their pain to others and includes catastrophizing, hoping/praying, retreating, using medications, and worrying. Active coping has been linked to less pain, depression, and better physical and psychological wellbeing. Passive coping, however, is associated with increased pain and depression.[85]

Coping is differentially associated with pain. Nevertheless, there are racial, ethnic, and sex differences in pain coping. In a meta-analysis of 19 studies, Meints and colleagues found that AA individuals engage in more coping overall than NHW individuals.[86] More specifically, AAs report greater use of passive coping strategies (e.g. hoping and praying and catastrophizing), whereas NHW individuals are more likely to use active strategies such as ignoring pain. Indeed, AA and Hispanic Americans pray more in response to pain than do NHWs,[86,87] whereas there are no differences between AA and Hispanic Americans for prayer.[88] Moreover, praying has been associated with greater pain severity, interference, and disability[89] and at least partially contributes to race differences in experimental pain.[87] A more granular look at the literature on prayer in response to pain has found that passive prayer (e.g. "God, take away the pain)" is associated with poorer pain tolerance than active ("God help me endure the pain") or no prayer.[90] Despite consistent race differences in ignoring pain,[86] this strategy has not been found to mediate AA-NHW differences in pain.[87] Furthermore, Mexican Americans, NA, and Asians are more likely to cope stoically.[91–93] Although the relationship between stoicism and pain has not been examined, it serves to reason that stoicism may be related to underassessment and undertreatment of pain.

There are also sex differences in pain coping that may play a role in sex-related differences in pain. For example, men are more likely to engage in distraction while women seek social support, use positive self-statements, cognitive reinterpretation, and increase physical activity.[94] There are mixed results related to problem- versus emotion-focused coping. In one study, women were more likely to engage in problem-focused coping or direct action.[95] In contrast, another study suggested women are more likely to engage in emotion-focused coping (e.g. venting or reinterpreting emotions, seeking emotional support), and men are more likely to engage in problem-focused coping.[96] Overall, it is clear that women use more coping strategies than men (e.g. more tools in their coping toolbox). However, some of the strategies more likely to be used by women may be associated with increased pain and dysfunction, which may help to explain sex differences in the perception of pain.

Catastrophizing

Catastrophizing is a cognitive and emotional response to pain characterized by rumination, magnification, and helplessness. Catastrophizing, sometimes considered a coping strategy[97] and

others a pain appraisal,[98] is associated with greater pain intensity, interference, and disability.[99] There is not only consistent evidence that women, AA, and Hispanic individuals catastrophize more in response to pain than men and NHWs,[100,101] but that catastrophizing mediates race and sex differences in pain sensitivity. Women and AA individuals catastrophize more in response to pain, which is associated with poorer pain tolerance. It is important to note, however, that catastrophizing may not be "all bad." According to the communal coping model of catastrophizing, catastrophizing may serve to maximize social proximity and support.[102] Women and members of racial and ethnic minority groups are often more social and, as a result, more likely to seek social support. This social inclination may explain the racial, ethnic, and sex differences in catastrophizing. Unfortunately, the increased pain behavior exhibited by those more likely to catastrophize is associated with poorer outcomes, including increased pain and disability, less solicitousness and more punishing responses from partners, and a poorer relationship with pain care providers.[103,104] Thus attempts to increase social support via catastrophizing may create a "double disparity," increasing pain sensitivity, social isolation, and resulting in poorer pain treatment.

Negative Affect

Negative affect, including depression and anxiety, are associated with increased experimental and clinical pain, disability, and a poorer quality of life.[105] The comorbidity between pain and depression has been well documented.[106] There is consistent evidence that depression is more prevalent among women than men,[106] and among people with depression, women are more likely to report pain.[107] Similarly to depression, women report greater levels of anxiety and more frequently experience anxiety disorders.[108] However, anxiety may be more strongly related to pain among men. In one study, anxiety was associated with pain sensitivity among men but not women.[109] Greater pretreatment anxiety predicted greater reductions in pain after interventional therapy for men, but not for women.[110] Similarly, negative affect also seems to explain some of the racial and ethnic differences in the pain experience. In a study of individuals with OA, AA individuals experienced greater negative effects than NHW individuals, which accounted for greater pain severity.[111] There are also consistent findings indicating that the link between emotions and pain is greater among AA than NHW individuals.[2,6] Perhaps the greater levels of negative affect experienced by ethnic and racial minorities alters their central pain processing, thus resulting in pain disparities. Indeed, Bulls and colleagues found that AA participants experienced greater depressive symptoms than NHW participants and that this was associated with greater temporal summation of pain, a measure of pain facilitation.[112]

Treatment Expectations

Patient expectations are an increasingly relevant topic because of the shift toward patient-centered health care and are positively associated with pain treatment outcomes.[113] That is, better treatment expectations are associated with better treatment outcomes. There is evidence, particularly in the context of joint replacement, that minority patients generally have poorer pain expectations[114] and that these expectations are associated with less willingness to undergo such procedures. However, there is a paucity of research assessing other racial, ethnic, or sex differences in treatment expectations and how those potential differences may influence outcomes.

Gender Roles

Gender roles of pain, the normative sociocultural response to pain that differs by gender, may also influence sex differences in pain. Masculine gender norms are associated with increased tolerance to pain among men, while feminine gender norms suggest pain is a normal part of life and, therefore, are more permissive of pain expression.[39] Studies have shown that these norms are associated with threshold and tolerance for noxious stimulation. Indeed, higher masculinity is associated with greater threshold and tolerance and lower pain ratings for noxious stimuli, while higher femininity is associated with lower tolerance.[115] Using the Gender Roles Expectations of Pain questionnaire (GREP), researchers found that both men and women considered women to be more pain sensitive, less enduring of pain, and more willing to report pain than the typical man.[116] There is also evidence that women view overt expressions of pain as more acceptable than men, explaining sex differences in cold pain.[117] It is important to note that gender roles of pain are malleable. When participants are given gender-based expectations for pain, sex differences in cold pain tolerance are no longer significant.[118]

Epigenetic Differences

Because of race differences in early life conditions, AA may likely experience epigenetic changes that influence racial differences in chronic pain.[119] Epigenetics, heritable changes in gene expression that do not alter the underlying genetic sequence,[120] result from several mechanisms including DNA methylation. DNA methylation, a chemical modification of DNA that regulates genetic phenotypes, is sensitive to environmental input. For example, environmental stressors such as adverse childhood experiences (ACEs), chronic stress, and low socioeconomic status are all more common among AA[121] and contribute to epigenetic changes via higher DNA methylation levels.[122] There is growing evidence that these epigenetic changes are associated with the development of chronic pain.[123] Indeed, greater DNA methylation is associated with chronic low back pain and fibromyalgia.[124] Thus environmental adversity, more common among racial minorities, leads to epigenetic changes that are but another mechanism of developing and maintaining ethnic and racial pain disparities.

Allostatic Load

Racial, ethnic, and sex differences in allostatic load may also contribute to pain disparities. Allostatic load, or the systemic stress on the body to maintain balance,[125] are associated with exposure to chronic stressors, including ACEs, trauma, discrimination, poverty, and chronic illness.[126] Although few studies have examined the relationship between allostatic load and pain, there is evidence that greater allostatic load is associated with greater headache prevalence, more reports of pain lasting more than 24 h, and greater widespread body pain, and greater chronic pain severity.[127,128] Because women and members of racial and ethnic minorities are more likely to experience significant life stressors, it is reasonable to presume that the resulting allostatic load may be contributing to pain disparities.

Hormones

In addition to gynecologic syndromes that lead to pain as well as greater female longevity, several other biologic factors contribute to sex differences in pain. Gonadal hormones can affect both the

peripheral and central nervous systems and influence the perception of pain. This is evidenced by age-related changes in pain prevalence that coincide with age-related changes in gonadal hormones and differences in pain perception across the menstrual cycle. For example, migraine and temporomandibular disorders (TMD) prevalence are similar between prepubescent boys and girls but then rises in women after puberty.[129,130] Similarly, migraine frequency and TMD pain are reduced during pregnancy while the severity of IBS-, TMD-, headache-, and fibromyalgia-related pain all vary across the menstrual cycle.[131] Postmenopausal women on hormone replacement therapy and women using oral contraceptives are at increased risk for various chronic pain conditions.[132,133] Further highlighting the association between estrogen and increased pain are results from a study indicating that approximately one-third of male-to-female transsexuals undergoing hormone replacement therapy develop chronic pain. In contrast, half of female-to-male transsexuals report improvement in chronic pain.[134] On the other hand, as estrogen rises during pregnancy, migraine and TMD pain decreases. Similarly, the sudden decrease in estrogen after pregnancy is associated with greater pain, stiffness, and the precipitation of migraine pain.[135]

Endogenous Opioid System

There are also sex and racial differences in multiple levels of the endogenous opioid system. Differences in the distribution, expression, and sensitivity of opioid receptors across race, ethnicity, and sex indicate this may be another biologic mechanism underpinning disparities in pain perception and response to treatment. For example, at rest, women show higher μ-opioid receptor binding than do men.[136] Moreover, women with high estradiol show higher brain μ-opioid receptor binding than women in low estradiol states.[137] In contrast, men show higher μ-opioid receptor binding in response to experimentally-induced muscle pain.[136] There are also sex differences in the metabolization of opioids.[138] Women have greater expression of the CYP3A4 enzyme and thus metabolize opioids such as fentanyl more quickly, resulting in less effectiveness. Men have greater expression of the CYP2D6 enzyme resulting in faster metabolism of and poorer response to codeine.[139] Differences in body composition may also affect blood concentrations of opioids. Because opioids are lipophilic and women have more body fat than men, women may have greater blood concentrations of opioids.[138]

Although less studied, there is also evidence there may be racial and ethnic differences in the endogenous opioid system, and these may contribute to the greater burden of pain experienced by racial and ethnic minorities. In a recent study examining race differences in μ-opioid receptor binding, Letzen and colleagues found that AA participants demonstrated greater opioid binding potential in cortical areas associated with pain processing (e.g. ventral striatum, insula, dorsolateral prefrontal cortex) than did NHW participants.[140] These results suggest that AA individuals' greater unoccupied μ-opioid receptor density may be related to less endogenous opioid binding, resulting in greater pain sensitivity. Furthermore, there is evidence that AA individuals demonstrate less endogenous opioid pain inhibition than NHWs, providing further support for endogenous opioid system functioning as another mechanism of racial and ethnic pain disparities.[141]

Central Nervous System Functioning

Functional imaging has provided evidence for sex differences in the central nervous system functioning in response to pain. For example, women show greater contralateral thalamus and interior insula response to heat pain than men.[142] They also show greater deactivation in the somatosensory cortex, insular cortex, and dorsolateral prefrontal cortex. In response to a laser heat stimulus, men show greater activation of the parietal cortex, secondary somatosensory cortex, prefrontal cortex, and insula, while women show greater activation in the perigenual and cingulate cortices.[143] Similar results have also been shown in patients with IBS. In response to visceral pressure created via a balloon catheter in the rectal colon, women show more activation of the ventromedial prefrontal cortex, the right anterior cingulate cortex, and the left amygdala.[144] In contrast, men show more activation of the right dorsolateral prefrontal cortex, insula, dorsal pons, and periaqueductal gray matter. While the nuances of individual and group differences in central nervous system responses to pain are still being examined, there is evidence to suggest that sex hormones influence the processing of pain-related stimuli. Indeed, a study of women using oral contraceptives with low testosterone levels showed reduced pain-related activation in pain inhibitory regions of the brain, including the rostral ventromedial medulla.[145] However, more research is needed to further elucidate the relationships between sex, gender, gonadal hormones, and cortical pain processing.

Discrimination & Bias

Perceived bias and discrimination may also contribute to racial disparities in the pain experience. The majority of AA and Hispanic people in the United States report that they have been discriminated against because of their race or ethnicity.[146] Such discrimination is a chronic stressor that may be associated with the development and maintenance of chronic pain.[147] Indeed, experimental studies demonstrate higher levels of perceived racial discrimination associated with greater pain sensitivity among AA with chronic pain.[148] Likewise, perceived discrimination is also associated with elevations in clinical pain severity among patients with chronic pain.[149] Thus it is important for providers to consider the role of their own biases and decades of structural racism in the experience of pain among minority patients.

Although overt discrimination is rare, Hoffman and colleagues found that medical students and residents held false beliefs about biologic differences between AA and NHW patients and that these were associated with racial bias in pain perception and treatment recommendations.[150] Moreover, Hispanic Americans and African Americans (HAs) and AAs with chronic pain report fear of discrimination based on their race/ethnicity when seeking pain care[52] and indicate that ethnicity and culture have affected their access to pain management.[151] Results of vignette-based studies have confirmed this. For example, patient race has been shown to influence providers' judgments of pain and their recommendation for pain relief.[152] While the specific mechanisms driving such bias remain unclear, there is evidence to suggests that racial biases in pain perception and treatment are due, at least in part, to implicit rather than explicit bias and are specific to pain rather than general bias.[153]

Patient Preference

Cultural differences across racial and ethnic groups may influence patients' treatment preferences. For example, 38% of HAs and 9% of AAs are concerned about taking too many analgesics, while 27% of HAs and 12% of AAs are concerned about side effects.[55] These concerns may be related to addiction. Indeed, AAs and HAs have a greater fear of addiction to pain relievers than do NHWs.[154] Even in terminally ill patients, minorities are more likely than

NHWs to refuse additional pain medications because of fear of addiction.[155] Additionally, minority patients may not believe in the efficacy of analgesics. Compared to NHWs, AAs believe pain medications cannot control pain[156] and instead rely more on other nonpharmacologic coping strategies. Similar to AA patients, Hispanic individuals are more hesitant to take pain medication.[20] This may lie in cultural norms of pain perception, in which Hispanic Americans are found to be more stoic and tend to bear more pain than NHWs.[20] Hispanic culture is family centric and holds a belief in overcoming pain unless completely unbearable. Culturally, Hispanics report that taking pain medication could be seen as a form of weakness. Additionally, Hispanics feel a stronger sense of responsibility toward caring for their family members and may inhibit seeking pain care out of fear that treatment may leave them unable to care for their family.

Communication

The experience of chronic pain involves frequent engagement with healthcare services and providers to treat or manage one's pain. Interactions with healthcare providers influence the degree to which patients feel empowered in managing their pain. While more frequent visits to the doctor's office are associated with greater pain, support from doctors in managing one's pain is associated with less pain overall.[157] Yet, many patients with chronic pain feel unsatisfied in their relationships with their providers. A meta-ethnography of qualitative literature on patient-provider relationships in pain-related care conducted by MacNeela et al. indicates that across studies, both patients and providers are dissatisfied with their relationships in pain management care.[158]

Patient-provider relationship dissatisfaction in pain management care may stem from poor communication, especially patient-centered communication. There are several ways patient-provider relationships demonstrate sub-optimal communication. In a review of communication problems, Ovretveit highlighted the consistent finding that providers might fail to create an optimal care environment which contributes to a breakdown in communication.[159] Problems in communication then reflect both provider and patient ineffectiveness.

Patients identify issues in communication, such as providers failing to take enough time with patients to fully listen to them and understand their experience and preferences for treatment.[160] Patient and providers can disagree on many areas of treatment, including the seriousness of the condition, barriers to care, the approach to illness management, treatment goals, and the importance of a definitive diagnosis. Additionally, providers may not communicate effectively in collaborative treatment planning. Breakdowns in communication can contribute to dissatisfaction among both patients and providers.[161]

When examining sex differences in patient-provider communication among samples of patients with chronic pain, women report more negative communication from their providers, which impacts their overall satisfaction with care. Women are more likely to experience comorbid pain conditions and, as a result, face more barriers in communication regarding the nature of their pain and treatment approach, leaving them feeling misunderstood by their providers.[162] In particular female veterans with chronic pain have identified that they feel their providers, especially ones who primarily treat men, display a worse understanding of their pain.[162] Additionally, women with fibromyalgia report encountering negative gender-based stereotypes related to being labeled as hypochondriacs when discussing disability claims with their providers.[63] Whereas NHW women may only rely on medical documentation for such purposes, women of color report having to engage in more moral-boundary work to legitimize their pain complaints and have them recognized as worthy of assistance.[63] In this way, providers require women of minority ethnic backgrounds to communicate in different ways to obtain the same resources as NHW women.

There are also racial and ethnic disparities in patient-provider communication. Racial and ethnic minority patients report more difficulty than NHW patients in communicating in ways that health providers understand and believe.[163] This may be particularly true in EDs where there are not established relationships and minimal time.[1] Indeed, when under time constraints, providers may be more reliant on stereotypes and heuristics, which in turn may impact communication with minority patients. Providers display less patient-centered orientation in their communication with AA patients and demonstrate greater verbal dominance[164] when compared to NHWs. Physician verbal dominance in conversations with AA patients is more likely to occur when providers endorse greater racial bias.[165] When providers perceive AA patients consistent with common AA stereotypes, they also demonstrate slower speech, less patient centeredness, and poorer quality interpersonal care. In contrast, providers who perceive White patients consistent with White stereotypes demonstrate less verbal dominance, faster speech, and person-centered care.[165]

Researchers have posited that differences in preferred language may be a barrier to effective communication,[166] particularly among Hispanic patients. Indeed, Hispanic patients are more likely than NHW patients to report that providers do not believe their pain.[163] Spanish-speaking Hispanic patients report believing that seeking care is more difficult because they speak Spanish and tend to seek care less often than Hispanic individuals who speak English. One reason for such difficulties may be the lack of Spanish-proficient providers in pain care and a lack of interpreter services.[167] Language barriers can also have a negative impact on the care of Hispanic patients during care. For example, Hispanic patients may experience difficulties describing their pain to providers or understanding treatment decisions and recommendations.[168] Overall, disparities in provider-to-patient communication strongly affect how patients engage with care. Providers unaware or unresponsive to cultural variation in the pain experience are more likely to interpret pain in terms of their own culture, which can adversely impact pain management.[169] Given these communication difficulties, it is not surprising that racial/ethnic minority patients prefer providers of the same race/ethnicity and report greater satisfaction with care when racially matched with their providers.[170]

Underreporting

The Institute of Medicine has documented that chronic pain is typically underreported, and this under reporting may be magnified among groups of individuals from minority backgrounds.[171] Pain may be underreported for a wide variety of reasons, including patient non-disclosure or because providers may not question patients about pain. Among racial and ethnic minority patients, non-disclosure may be indicative of cultural beliefs about reporting pain and distress. For example, 21% of AAs report difficulty talking to their provider about cancer pain. Moreover, 57% of AAs and 38% of Hispanic Americans report that providers did not ask about their pain.[172] Hispanic and NA specifically hold culturally-bound beliefs regarding disclosure of pain. For example, NAs do not like to talk about themselves, complain about pain, or ask for

help. Moreover, when they ask for help and their needs have not been met, they will often not voice this until the pain is severe.[93] Among Hispanic individuals, pain is often faced with stoicism, although there seems to be an influence of sex.[92] While Hispanic men and women both report pressure to withhold disclosing pain, men endorse "machismo" or a sense of masculinity while women forgo their own needs to prioritize their family. Hispanic individuals may also refrain from reporting pain to their health care providers because they view pain as a natural consequence of their condition or a punishment from God. Together, such under reporting of pain may play a critical role in the undertreatment of pain among minorities.

Access to Care

Limitation in access to care remains a great public health issue that plagues the healthcare community. However, in this section, we will discuss access to care in relation to racial and ethnic disparities in pain relief. Systemic factors affecting patient access to care are inextricable from race and ethnicity. Minority groups are more likely to be of lower economic standing and thus live in areas in which there are fewer hospitals or pharmacies.[173] Even when minorities have access to pharmacies, they may not be able to get their prescriptions locally. Studies have shown that pharmacies in White neighborhoods are better stocked with opioids than minority non-White neighborhood pharmacies that tend to stock fewer medications.[174] In fact, 50% of randomly selected New York City pharmacies did not have adequate opioid analgesics in stock.[175] The study further showed that pharmacies in predominately Hispanic and AA neighborhoods were less likely to stock opioid analgesics than NHW neighborhoods.

Minority groups also have a more difficult time accessing specialty providers such as tertiary pain clinics. Thus AAs are more likely to present with pain in emergency rooms than their NHW counterparts.[174] Access to high quality pain care is also related to disparities in access to health insurance. AAs and Hispanics are more likely to be on a government funded healthcare insurance provision than NHWs. They are also more likely to be underinsured, making access to pain relief more difficult.[176] In addition, nearly half of Hispanics and one-third of AAs with chronic pain report financial concerns prevent them from getting their pain treated.[52] Taken together, it is clear that access to quality and appropriate pain treatment is disparate across racial and ethnic groups, an issue that significantly contributes to the unequal burden of pain.

Conclusion

Although pain is a pervasive problem, the burden of pain differs by race, ethnicity, and sex. Various biologic, psychological, and social factors have been identified as contributing to disparities in pain experience, report, treatment, and outcome. At this point, it seems insufficient to merely continue conducting research that identifies and quantifies these disparities. Instead, future work encompassing clinical research, service delivery, and healthcare practice should focus on mitigating the above-described contributing factors to diminish disparities in the experience and treatment of pain, improving the experience of pain care, and optimizing the diagnosis and management of pain for all sufferers. While some factors may not be modifiable (e.g. hormones, endogenous opioid system), providers must understand their role and adopt an individualized approach to pain management that considers them.

Key Points

- Despite the universality of pain, the burden of pain varies across race, ethnicity, and sex.
- Racial and ethnic minorities and women have greater pain prevalence and severity and are more likely to have their pain underestimated and undertreated.
- While there are some biologic determinants of pain disparities (i.e. hormones, endogenous opioid system, and central nervous system functioning), psychosocial factors seem to play an important role.
- Although disparities are examined on a group level, providers must use an individualized medicine approach to be aware of and reduce disparities whenever possible.

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12

Communication and Clinician Relationships to Improve Care for Patients With Chronic Pain

DAVID J. TAUBEN, MARK D. SULLIVAN

Introduction

In March 1927, Dr. Francis Peabody, Harvard Medical School educator and Boston surgeon, published a seminal article in the Journal of the American Medical Association with the oft-quoted maxim, "One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."[1] Caring, by optimizing therapeutic relationships between clinicians and patients, has since been characterized as the practice of "patient-centered" medical care.[2] In 2001, patient-centered care was described by the National Academy of Medicine's (formerly Institute of Medicine) *Crossing the Quality Chiasm: A New Health System for the 21st Century* as "respectful of and responsive to individual patient preferences, needs and values, and ensuring that patients' values guide all clinical decisions."[3] Patient-centered care consists of two essential components: 1) taking the patients' perspective on their illness and their life and 2) activating the patient for self-care.[4] Both of these components are essential in the care of patients with chronic pain.

All clinically directed health care involves interpersonal interactions of patients with their treatment providing clinicians. So, why is this therapeutic relationship especially important in the context of caring for patients with chronic pain? Chronic pain, a biopsychosocial condition, by its very nature, includes more than just a straightforward communication of biomedical objective information. Unlike some other medical conditions, pain is not itself visible. Therefore individuals with chronic pain often struggle to have their condition recognized and legitimated. The comprehensive assessment and effective treatment of chronic pain also entails an understanding of its impact, so we must also understand our patients within the broader context of their pain experience and how they see themselves managing, or more likely struggling, with their persistent and intrusive painful sensations. This includes relationships with families and communities. It also includes managing home and work responsibilities and striving for life goals that offer meaning and purpose in their lives.

Hearing the patient identify personal goals of pain care and providing a space and an opportunity to comfortably disclose their beliefs and expectations and how it is that they *really feel* means that the management of patients with chronic pain requires a trusting relationship with a clinician. This type of relationship requires communicating with patients in their own words and recognizing their behaviors from their unique perspectives, and also by acknowledging that their pain is "real." Treatment relationships begin with therapeutically effective communication. This chapter will describe why empathic communication is especially important for chronic pain management, how a strong therapeutic alliance can improve chronic pain care outcomes, and what specific clinical competencies have been demonstrated to improve patient engagement in their treatment.

Listening and Narrative Medicine

In 2010, Eloise Carr, RN PhD, a researcher studying patient experiences of chronic pain, recalled a patient's statement: "Stop trying to cure me and start listening."[5] Clearly, this individual's prior experience of pain treatment did not include "being heard." Being heard means being acknowledged. Being heard means being understood. Listening to the patient is fundamental to establishing the clinician-patient relationship.

However, *demonstrating* that you have listened and that you understand is another essential part. Check with your patient if you have understood their predicament with their pain. Restate what you have heard and ask the patient if you have it right. Acknowledge the pain and its impact on their life. When pain becomes chronic and therefore complex, objective physical exam findings, imaging, and laboratory studies are insufficient to capture the nature and effects of the illness for the patient. Patient self-reported pain intensity has long been a component of chronic pain evaluation.[6] But it is a gross oversimplification of a chronic illness and leaves many questions unanswered. In 2014, an undergraduate journalism major enrolled in an elective course titled "Pain" was asked, "What does 12/10 pain intensity mean?" He replied, "Maybe the patient is shouting."[7] So, with a maximum score of "10" to rate an unimaginably severe pain experience, this "unheard" patient felt there was no other option than to increase the numeric volume to "12/10." A patient who feels understood will be more likely to trust their provider, be more likely to follow suggested treatment recommendations, and be more satisfied with their care.

Communication begins with an *action*, such as a patient sending a message of distress, followed by an *interaction* whereby the

physician responds with a message of understanding, and a *transaction*, such as commitments to a future course of action.[8] The style and techniques for effective listening will vary based on the differences of personality, temperament, and cultural and racial experiences of clinicians and their patients. Communication is also much like a dance since each partner strives to follow the other's cues. Although conversations with patients struggling with chronic pain do follow a classical choreography, it often requires a jazz-like improvisation.

Published recommendations now call for a wider range of questions beyond quantification of pain intensity, including interference with function, enjoyment of life, sleep, mood, treatment expectations, and goals.[9] Above all, patients want to tell the story of their pain, and they want to know that their clinicians have understood it. Chronic pain is experienced within an individual's unique life events, preformed and yet changeable social context, and subjective cognitive and emotional states.[10] Pain neuroscience researchers describe a so-called "dynamic pain connectome" based on fMRI evidence of "brain-wide network communication on multiple timescales," and that "attentional states are in constant fluctuation."[11] According to pain neuroimaging researcher Irene Tracey, "Pain is not a unitary thing, and no two pains are the same, even in the same individual."[12] Scientific medicine relies upon measurement to both diagnose and track treatment outcomes. Without specific biomarkers that can describe, record, measure, and track the variable and dynamic human experience of pain, validated patient reported outcome questionnaires are necessary.[13] So too is listening.

The biopsychosocial evaluation and treatment of chronic pain also depend upon an in-depth exploration of the patient's own beliefs and attributions, what *it is* they understand to be causing their pain and why it persists even after extensive biomedical evaluations and many treatments have been tried and failed. What does the patient believe to be the cause for their persistent pain? It may be that the cause for their pain has so far simply been missed. Why do they believe prior treatments have failed? It may be a conviction that their prior doctors just do not know, or worse, do not care. What are their worries? Often it is being told "*there is nothing left to be done*" or thinking, "*it's all in my head.*" What might other family members and friends be thinking? Maybe "*I'm just making it up*," *"I'm a burden on everyone,"* or "*I'm not someone they want to be with anymore.*" What expectations will define a successful outcome? Maybe the doctor "*could do the correct surgery*," the "*right procedure*," or prescribe the "*best medication*" and everything would be how it was before their pain began. What else is going on in the patient's life? Might it be: "*All my time is spent finding a way to get better," or "Since nothing else matters but my pain, there's no point in planning ahead*"? What are the patient's own goals? It is important to know whether it is to become pain-free or if it is to be able to return to improved function and begin to recover their life. Since many pain treatments will require an effortful and patient-directed commitment to a range of behavior changes and self-management approaches, treatment will need to be tailored to the patient's perceived needs and hopes. Interpreting pain, function, and mood numeric ratings are, of course, important. For many complex chronic pain presentations, such as those more complex patients referred to pain specialists, much depends upon the patient's own story. Pain, a biopsychosocial condition, requires more than just the "medical story." Knowing how patients experience their pain requires effective patient-centered communication. The mystery is in the history.

Clinician-Patient Relationships: Empathy and Therapeutic Alliance

Empathic listening to the patient's story using the techniques of "narrative medicine" is a long established approach to advance care and improve chronic illness treatment outcomes.[14] "Not only is diagnosis encoded in the narratives patients tell of symptoms but deep and therapeutically consequential understandings of the persons who bear symptoms are made possible in the course of hearing the narratives told of illness."[15] Intentional and directed attention to what our patients say, *active listening* is not merely kind and courteous but will increase the likelihood of a more effective treatment outcome. Effective communication explicitly acknowledges patients as persons: "The clinician must know the patient well enough to be able to answer the patient's question 'What would you do, if you were me?'"[16] Empathy is commonly described as the ability to understand the inner experiences of patients, to communicate this understanding, and to respond therapeutically.[17] Empathy is distinct from sympathy. Sympathy names the ability to feel someone else's emotions, especially by feeling sad about their misfortune. Empathy names the ability to understand other people's feelings as if we were having them ourselves.

Empathic listening and compassionate clinical care date to antiquity, long before medicine had developed as a scientific profession (e.g. Hippocrates, 5th century BCE: "Cure sometimes, treat often, comfort always"; Ovid, 1st century: "When the mind is ill at ease, the body is affected.") More recently, Abraham Verghese, physician and author of the widely acclaimed 2009 novel *Cutting for Stone,* wrote, "'Tell us please, what treatment in an emergency is administered by ear?'…I met his gaze and I did not blink. 'Words of comfort'…."[18] The same unblinking response applies to clinicians caring for patients with chronic pain, which for many patients represents an unrelenting emergency.

Modern scientific medicine has since elevated the role of clinical objectivity and technical competency. However, technical access to objective disease can displace empathic concern for what our patients tell us about their individual illness experience. This competing tension has reportedly led to an overall decline in empathy as trainees progress through medical school and residency training.[19] Efforts are underway in medical school curricula to improve medical student empathy and narrative competency,[20,21] but these efforts encounter competition for space in the crowded time to cover other crucial biomedical topics, technical competencies,[22] and other recommended pain topics.[23]

Empathy, in its most basic form, is described as "emotional contagion," characterized by unconscious state-matching (the contagious yawn!). Neuroimaging studies in humans,[24] and even electrophysiologic[25] and behavioral findings in rodents,[26] suggest that empathy for pain is evolutionarily conserved. Therefore we are hard-wired for empathic behavior; we need only harness this natural capacity to show that we understand *our patients' feelings* as if *we were having them ourselves.* The significance of empathy is even more striking in pain medicine since chronic pain is a complex social phenomenon that often leaves individuals with chronic pain socially isolated from family and friends and feeling misconceived and misunderstood by their doctors.[27] Neuroscience research has shown that social exclusion and physical pain also share neuroanatomic structures and functions.[28] The clinician has a unique opportunity to provide a "social buffer" that, even in the absence of any other intervention, may positively impact the patient's pain experience.

In a busy clinic setting, it is challenging to take adequate time to listen, sit down, look directly at our patients rather than their electronic health record, and not interrupt patients who may be attempting to understand our questions. However, it is possible to allow more time by scheduling longer or more frequent visits or by dedicating periodic visits to pain exclusively so as not to be distracted by the many other general health and preventative medicine concerns also needing attention. If such measures are not feasible, we can introduce even very brief breaks from our intensive data-gathering agenda to practice active listening. Look our patients in the eye; patients notice these actions, particularly those who have had a long history of feeling ignored. Listen without judgment and pay attention to nonverbal cues. Take a few moments to paraphrase what we have heard and demonstrate to our patient that they have been heard. If we fail to listen, patients may register negative feelings of clinicians' disinterest and disdain rather than empathic concern, in other words, "They don't want anything to do with you."[29] Hurried and tightly scheduled primary care and pain specialty practices are challenged by system-related (e.g. too little time[30,31]), patient-related (e.g. difficult communication,[32] particularly when opioid management is involved[33]), and physician-related barriers (e.g. compassion fatigue[27]) that may lead to reduced empathic behaviors. Empathic failure can reduce patient satisfaction and compliance with treatment guidelines, worsen clinical outcomes, reduce ratings of clinical competence, and increase burnout, medical-legal risk, and overall healthcare costs from excess diagnostic test expenditures.[34] Demonstrating empathy may also improve the accuracy of clinical decisions since pain related medical decision making is so often based on personal features and values of the patient that extend beyond objective medical evidence.[35]

Expectations Influence Pain

The patient expectation of pain relief is among the leading causes of placebo analgesia and associated with many of the described psychological and neurophysiologic mechanisms of placebo response. Placebo analgesia response has been proposed to be a form of "top-down" conditioned modulation, an "evolutionary imperative to optimize the selection of future actions" in response to "bottom-up" peripheral pain sensations that may or may not represent potential bodily injury.[36] There is extensive literature on neurophysiologic and behavioral mechanisms of placebo analgesia studies, including several recent excellent reviews.[37,38] Nocebo response, the experience of a *negative* response to an otherwise inactive treatment, is also conditioned by expectations. Nocebo response can be predicted by prior lack of response, adverse events, or even negative outcomes following prior ineffective medication, behavioral health, physical therapy, or surgical treatments. Any time spent is well invested when patients better understand their condition, share expectations of their treatment, are provided clear instructions, and shared goals are communicated in advance of treatment delivery, whether it be medication, behavioral health interventions, physical therapy, or procedural management.[39,40]

Taking a step further, setting realistic expectations in advance of initiation of pain treatment "*-any treatment-*" would then be likely to predict more favorable treatment outcomes. Cheerfulness and unfounded optimism can lead to patient and clinician frustration and further disappointment when new or different treatment approaches are not met with immediate positive results. How can we determine what our patients expect? Since patient and physician expectations of pain treatments are frequently not aligned (e.g. just temporary relief from local anesthetics, only modest response to a gabapentinoid or serotonin-norepinephrine reuptake inhibitor, or delayed benefit from cognitive behavior or physical therapies), it is important to understand what the patient expects treatment to accomplish and how long it may take to perceive benefits.[41,42] Favorable treatment outcomes can result as much from the pharmacologic activity of a drug, the technical precision of an interventional procedure, or the specific physical therapy modalities as from the clinicians' method of communication delivery. The nocebo response is also relevant. An otherwise potentially effective treatment that had been previously tried and "failed" because of minor initial side effects may have become unacceptable and indefinitely rejected by the patient. By establishing trust using empathic communication and acknowledging prior side effects, resetting expectations with a very gradual upward titration may find a prior unsuccessful treatment to be well tolerated and effective. Similarly, reframing "failed" behavioral health or physical therapy by explaining a clear rationale and establishing patient-centered goals may overcome prior objections. Being heard and being understood matters across all domains of chronic pain management. So, pain treatment outcomes—positively or negatively—will be significantly affected by what we say to our patients, how we say it, how it is understood, the confidence we have earned, and the overall quality of a shared therapeutic alliance.

Patient-Centered, Shared Decision Making

Patient-centered, shared decision making is a widely advocated clinical practice intended to improve patient adherence, satisfaction, and clinical outcomes across many disciplines.[43–45] Based on the assumption that patients are experts in their own experience of disease, patient-centered care is especially relevant for the uniquely personal experience of chronic pain that is often biomedically invisible. Patient-centered means that the care has solicited and included the patient's personal goals of treatment. However, shared decision making in chronic pain treatment presents unique challenges since pain science remains poorly understood by both patients and many care providers and much depends upon self-motivated patient self-management activities (e.g. behavioral and physical therapies). This is, in contrast, to passively delivered drug administration and surgical treatments effective for many other common chronic medical conditions. In addition, non-opioid treatments and procedural interventions often provide less than hoped for pain relief and remain highly dependent on concurrent long-term patient commitment to behavioral, fitness, and lifestyle modifications. Furthermore, while opioids unquestionably provide significant relief for acute and perioperative pain, their effectiveness in chronic non-cancer pain is not proven for many commonly occurring pain conditions, and their side effects and management risks are significant.[46] Opioid prescribing for chronic pain does represent a challenge to patient-centered, shared decision making since it is the clinician, NOT the patient, who ultimately controls prescribing. Notably, published United States opioid guidelines for chronic pain recommend clinicians should "collaborate" and "*empathically* review benefits and risks…" and should *offer to work with the patient.*[47] Regardless, patient-centered shared decision in chronic pain remains important and possible.

An individual who understands why chronic pain persists despite normal tissue healing and who is knowledgeable about treatment risks and benefits is more capable of active participation in informed patient decision making. This will require time and

effort dedicated to straightforward patient-level education about basic neurobiology and neurophysiology of pain processing by the nervous system that is both accessible and understandable to be truly patient-centered. There have been increasing numbers of popular self-help books and online resources that can be recommended and may be helpful to support in-clinic pain education for patients and families.[48–52] Neuroscience education for patients with chronic musculoskeletal pain disorders has been demonstrated by physical therapists with a positive effect on pain, disability, catastrophizing, and physical performance.[53] Evidence also supports the benefits of neuroscience education in chronic low back[54] and spinal pain.[55] Even very brief in-clinic physician and/or nurse or social worker directed education followed by recommended online, in-print reading or audiobooks improves adherence to drug and non-drug treatments, engagement in self-motivated pain-relieving behaviors (e.g. exercise initiation, pacing, relaxation techniques), and compliance with referrals for behavioral counseling can be beneficial.

Motivational Interviewing

Motivational interviewing (MI) is a well-established interview technique, initially developed as a systematic approach to engage patients in substance abuse treatment.[56] MI explores the gap between the patient's own aspirations for health behavior change and their current health behaviors. MI is intended to identify and develop patients' own motivations to change self-defeating behaviors. By exploring internal conflicts about the patient's values and behaviors, MI aims to uncover ambivalence about behavior change (e.g. physical exercise, sleep hygiene, medication, and healthcare seeking) and discover the patient's own motivations for change.[57] MI depends upon an active listening technique and a systematic and responsive approach to questioning intended to promote patient recognition of self-identified specific obstacles to achieving their own stated goals using their own words. MI is more applicable in difficult opioid prescribing situations than shared medical decision making since solicitation of the patient perspective is crucial, specifically the life goals and health aspirations that are part of an MI conversation. Although MI techniques have been most widely used in substance abuse care, they can be readily deployed in other aspects of pain medicine because engagement in self-management is essential if patients are to improve sleep, fitness, and diet. MI is directly linked to narrative pain management:

> *Intrinsic motivation for change arises in an accepting, empowering atmosphere that makes it safe for the person to explore the possibly painful present in relation to what is wanted and valued. People often get stuck, not because they fail to appreciate the downside of their situation, but because they feel at least two ways about it. The way out of that forest has to do with exploring and following what the person is experiencing and what, from his or her perspective, truly matters.*[58]

DiClemente and Velasquez frame the link between MI and the *stages of change* "through which people pass as they change a behavior."[59] They also provide a very useful verbal script for pain clinicians: "How has your pain changed you as a person, or stopped you from growing, from moving forward?" Since chronic pain cannot be separated from the person who has it, the clinician's task is to engage the patient to become the agent of their own change.

MI may be particularly useful when introducing the option of tapering and discontinuing opioids and other controlled substances because many patients are ambivalent about continuing on long-term opioid therapy and may benefit from MI techniques for patients to self-identify opioid related problems.[60] At times, MI can be effective in de-escalating difficult conversations, a well-recognized challenge in clinician-patient communication,[32] since the mere mention of de-prescribing medications can generate negative and confrontational interactions.

The use of a multidimensional tool at initial clinical assessment and then tracking change at every visit provides consistent opportunities to identify patient-reported outcomes (PRO) that are well suited to introduce specific domains for motivational change are especially valuable.[13] Though there are many ways to introduce MI into chronic pain conversations, eight PRO items measured by zero to ten numeric rating scales that are easily understood and have been very well accepted by patients can be used to facilitate the process. These include the three item PEG tool (i.e. pain intensity, pain interference with the enjoyment of life, pain interference with general activity),[61] two items about pain interference with sleep initiation and sleep maintenance, and the four item Patient Health Questionnaire (PHQ-4),[62] which assesses symptoms of anxiety and depression. At the initial visit, the clinician can review these items with patients asking them to identify which of these eight areas of their life they could possibly change. When pain intensity exceeds seven out of ten, a shared agreement can be developed when the status quo is not working. Other items can be viewed, and the clinician can seek shared agreement on which area they prefer to tackle first (e.g. poor quality of life, poor function, poor sleep, poor mood). Sleep disturbance is exceptionally common in chronic pain; nonpharmacologic options can be offered (e.g. sleep hygiene), and consider other potentially effective non-sedative hypnotic sleep medications (e.g. melatonin, low-dose tricyclic when appropriate). If patients choose to tackle general activity, possible ways to accomplish that (e.g. short walk, aquatic therapy, slow-paced targeted physical therapy) can be shared. Asking patients for their own interpretation of their outcomes by acknowledging that their time and effort are valued and that the information they shared will guide your shared treatment decisions. Table 12.1 delineates a four step approach, modified from Lussier and Richard's step-wise "communication tips" for nonpain-related topics applicable for motivating patients with chronic pain to behavior change.[57] Reducing pain intensity is the least likely to change, a trailing indicator of success, and so clinicians should do their best to steer patients away from expecting a reduction in pain intensity as their first step goal.

TABLE 12.1 Sample "Tips" for Motivating Patients to Change Behaviors to Improve Management of Chronic Pain

1. Is the status quo working?
Examples: "How does poor sleep/fitness /anxiety/depression/sedating or opioids medications affect your life?"
2. Is change possible?
"How do you think you might be able to get better sleep/become fitter/feel less depressed/take fewer pills?"
3. Can change happen?
"I see that you are now sleeping better/exercising more/seeing your therapist/taking fewer pills."
4. Coach to sustain change
"How can you keep going with your sleep/fitness/therapy/medication taper plan?"

Enhancing Clinician-Patient Relationships With a Collaborative Pain Care Model

Both pain experts and primary care providers often find it difficult to "be with" patients demonstrably suffering from chronic pain. Making this a satisfying line of work and avoiding burnout by working as a pain management *team* is very helpful. Incorporating a collaborative care model within multi-disciplinary pain management practice promotes improved communication by deploying a team of interprofessionals, who can then share the challenges and reduce the requirements for a medically trained pain expert to singlehandedly deliver emotional and social communication. A coordinated team of experts from multiple disciplines (e.g. medicine, psychology, physical therapy, social work, nursing, pharmacy), who share the same understanding of the interacting biopsychosocial dimensions of chronic pain, communicate effectively across their interprofessional competencies and keep *caring* for the patient as a common goal, will indeed have a positive impact on pain treatment outcomes.

Summary: Putting It Into Practice

The long history of the healing arts is founded on communication, caring, and compassionate listening. Acknowledging patients by empathically listening to their stories, narratives, and medical history is key to effective communication. Being with and sitting alongside patients as conversation partners and lead with open-ended questions since a therapeutic alliance arises from two-way conversations. Affirmation of patient progress toward their goals is key to motivating patients to continue to engage in changes necessary to improve their lives in the face of pain. At times fear, anger, and tears may be unavoidable, yet consolation may require just your silent presence and behaviorally communicated empathy. A few words of comfort may be all that is necessary, an acknowledgment that they are not alone and that their pain and suffering are not misunderstood. Remember that empathy is the ability to *understand* other people's feelings *as if* we were having them ourselves. However, they are not our feelings; they are theirs. A senior colleague from decades ago, recovering from protracted cancer treatment, once said, "It's always better to be the doctor than the patient." We are reminded of this when encountering a quagmire of anger and tears and then redirect this flood of emotions to deliberative clinically proven approaches that can offer some hope of relief and promote healing.

Ideally, a clinician's practice setting is already set up as a collaborative care model and includes a team of interprofessional pain care providers so that a nurse care coordinator, clinical psychologist, or clinical social worker can step in to help, so you would have no need to run away from an upset patient, and instead to redirect care temporarily to another qualified member of your pain care team. Although it is ideal to have an interprofessional pain care team embedded within one's practice setting, when such a team is not available, an effective alternative is to maintain a readily available, vetted, updated, and shared list of other appropriate community-based clinicians knowledgeable, skilled, and interested in the collaborative chronic pain care of your patients. A physical therapist focused on sports medicine and postoperative orthopedic rehabilitation may be unhelpful or may even frighten patients away from exercise of any kind.[53] Similarly, a psychologist focused on insight alone or supportive counseling approaches may omit important cognitive and behavioral skills addressing negative thoughts about pain, goal-setting strategies for structured behavioral activation routines, and communication strategies around pain related difficulties, which have been shown to be particularly important.[50]

To successfully care for those who present after months to years of chronic pain, exhaustively evaluated, seen by many other clinicians over many years without alleviation of symptoms, with the stigma of "a chronic pain patient," and without hope is no small challenge. To help to make a change in the lives of patients with chronic pain and to hear "thank you for giving me back my life" is a remarkably satisfying experience for patients, their families, and, of course, for clinicians. Improved communication skills that emphasize the patient perspective and leverage our natural empathic abilities can and do improve the care and outcomes for patients with chronic pain. Moreover, for successful pain clinicians, nothing is better than that.

Key Points

- Management of chronic pain, a biopsychosocial condition, by its very nature, includes more than just a straightforward communication of biomedical objective information.
- Patient-centered chronic pain care consists of taking the patients' perspective on their pain and activating the patient for self-care.
- Shared medical decision making aims to align therapeutic goals, improve patient treatment engagement, and support an agreed upon self-management plan.
- Narrative medicine communication skills such as empathic, reflective listening, and use of nonjudgmental language endeavor to strengthen clinician-patient therapeutic alliance, improve treatment acceptability and compliance, and increase patient and clinician satisfaction with pain care.
- Motivational interviewing (MI) challenges patient behaviors by contrasting these with patient aspirations. It can be used to change interfering behaviors such as poor sleep hygiene, insufficient exercise, inconsistent treatment adherence; and is particularly useful when tapering and discontinuing opioids and other controlled substances.
- A collaborative care model can improve communication by deploying an inter-disciplinary team who share the same understanding of the interacting biopsychosocial dimensions of chronic pain. This can reduce requirements for a medically trained pain expert to singlehandedly communicate and deliver all aspects of complex chronic pain care.

Suggested Readings

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Pharmacogenetics in Pain Management

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CASE 13.1

A 58-year-old Asian-American male with no other significant past medical history presents to the clinic with acute herpes zoster in the left T4 dermatome. The patient endorsed severe localized pain and tactile allodynia associated with a vesicular eruption. After three months, the rash resolves, but he complains of severe burning pain, allodynia, and hyperalgesia in the left T4 dermatomal region, suggesting that he has developed post-herpetic neuralgia (PHN). Nortriptyline 10 mg was prescribed, but shortly after starting the medication, he developed severe sedation, orthostatic hypotension, and xerostomia. Nortriptyline was then discontinued, and tramadol was initiated. However, the patient did not tolerate tramadol either. A third medication was then trialed hydrocodone/acetaminophen, but yet again, the patient responded poorly. Lastly, gabapentin 300 mg nightly was prescribed and titrated over several weeks to a target dose of 1800 mg/day in three divided doses. This medication slightly alleviated the neuropathic pain, but it was still not well-controlled, and the patient return for further assessment and treatment. It took over six weeks to select and titrate a medication that achieved any notable pain reduction in this specific patient.

This patient was treated according to available evidence-based guidelines,[1–3] yet he did not obtain adequate analgesia from the prescribed medications. Clinicians recognize that each individual patient responds differently to pain itself, and in the same fashion, response to medications varies from person to person. Advances in pharmacogenomics can help providers understand how genetic variations affect drug metabolism and response, thus offering clinicians the opportunity to identify the most appropriate pharmacotherapy before prescribed and improve patient-specific outcomes. Appropriate knowledge and utilization of pharmacogenomics can allow for the individualization of medication selection.

In the case described, the patient's inadequate pain relief requires a careful evaluation of the potential reasons rendering the medication ineffective. For example, nonadherence, drug interactions, pain mechanism, or a combination of these could be factors limiting medication efficacy. It is also important to consider the patient's genetic makeup affecting medication metabolism, thus impacting efficacy and toxicity. This is where pharmacogenomics can play a crucial role in pain management. The case illustrates the variable response and adverse event profile that might be observed when analgesics are prescribed. As noted, clinicians are keenly aware of how often individuals may not obtain the expected therapeutic benefit from analgesic medications across several pharmacologic medication classes.[4]

The response rates in well-designed studies of various analgesic therapies are approximately 55%. This "treatment success" rate is muddled by favorable analgesia to placebo.[5] A large number of patients will not respond to initial therapy. Many key areas of medicine are similarly affected by poor responder rates in clinical trials of diverse drug types. A clear understanding of how pharmacogenomic factors influence the effect of a prescribed analgesic could allow clinicians enhanced analgesic treatment outcomes.

The Impact of Pharmacogenomic Research on Clinical Medicine

Pharmacogenomics is the study of the impact of genetics on pharmacotherapeutic responses and tolerability. It is used to improve drug safety and efficacy through genetically guided, individualized treatments.[4] As previously noted, the same drug can be associated with different clinical responses among various populations. This is because each individual's unique genetic composition (i.e. genotype) provides the blueprint for the generation of singular protein expression profiles (i.e. phenotype), which subsequently leads to functional variations observed as clinical responses. Considering such genetic predisposition and receptor subtype expression can result in improved outcomes or resolution of disease. This approach is undoubtedly at the core of personalized medicine. When the clinician is aware of a patient's genetic predisposition and receptor subtype expression, this knowledge may lead to more individually focused prescribing with improved efficacy and safety for the patient.[4] Key terms used in pharmacogenomics can be viewed in Table 13.1.

The utilization of genetic information in clinical practice has far-reaching implications. The benefit of utilizing information derived from pharmacogenomics in the future of clinical medicine may lead to improved success rates, decreased side effect burdens, and reduced healthcare costs.[6] For example, the clinical integration of genetic information is routinely used in oncology to guide treatment.[7,8] Other areas of medicine are also beginning to tailor pharmacotherapies based on an individual's genetic information, and certain biomarkers are now known that can help guide treatment in many areas of medicine, including pain

management and rheumatologic diseases.[9] Pharmacogenomic testing has benefited patients and clinical medicine in general by improving the ability to stratify the risks of various treatments for individual patients by identifying groups of patients with a higher potential for poor efficacy or for adverse treatment effects (Table 13.1).[6]

The most commonly observed DNA sequences of a gene are termed "wild-type," and the less common alleles are "variants" if they occur in more than 1% of the population. The even less prevalent alleles have another name; DNA sequences in genes found in less than 1% of the population are called "mutations."[10]

Pharmacogenetics can allow clinicians to predict medication's pharmacokinetics and pharmacodynamics and can also help identify patients who are more prone to certain genetically associated diseases. For example, within pain management, an autosomal dominantly inherited peripheral neuropathy, hereditary sensory, and autonomic neuropathy type I confers insensitivity to pain mediated through the progressive degeneration of the dorsal root ganglia and motor neurons as the result of mutations within a specific location in chromosome 9.[11,12] Individuals with this genetic background cannot perceive pain, making them particularly prone to painless but potentially severe injuries, with detrimental complications, such as chronic skin ulcers and distal amputations. Kirsh and colleagues studied the polymorphism of a population in Louisiana by administering pharmacogenomic testing to all new patients. Based on 388 tests conducted, 42.3% of individual tests were extensive metabolizers (normal), 25.5% were intermediate metabolizers, 7.2% were ultra-rapid metabolizers, and 7.0% were poor metabolizers; 18% exhibited indeterminate results from inadequate DNA samples or unknown polymorphism. The authors noted that the study yield abnormal pharmacogenetic testing in nearly 40% of patients. In contrast, some studies have found that 83% of patients have abnormal CYP450 defects compared to 20% to 30% of the general population and that other sources found results consistent with the population of Louisiana studied. The growing body of evidence indicates that polymorphism can vary even among subpopulations, thus limiting the generalizability to other pain clinic samples.[13]

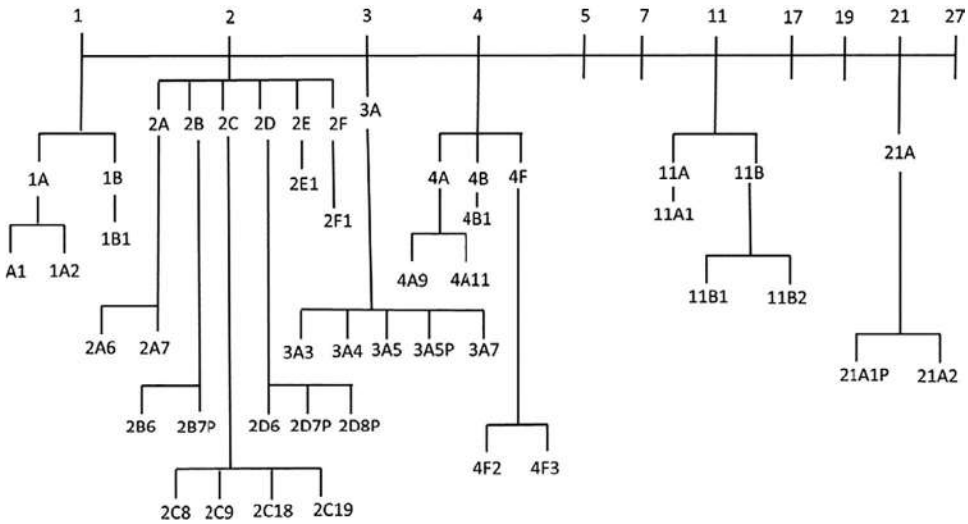
TABLE 13.1 Key Pharmacogenetic Terminology

Genome	The entire collection of genetic information (or genes) that an organism possesses
Genotype	The genetic constitution of an individual, either overall or at a specific gene
Heterozygous	The presence of two different alleles (one on the maternal chromosome and one on the paternal chromosome) at a gene location
Homozygous	The presence of two identical alleles at a gene location
Isoform	A variant in the amino acid sequence of a protein
Messenger RNA	An RNA-containing single-strand copy of a gene that migrates out of the cell nucleus to the ribosome, where it is translated into a protein
Mutation	A rare variant in a gene, occurring in less than 1% of a population
Pedigree	A diagram depicting heritable traits across two or more generations of a family
Phenotype	The observable characteristics of a cell or organism, usually resulting from the product coded by a gene (genotype)
Polymorphism	The existence of two or more variants of a gene in a population, with at least 1% frequency of the less common variant
Prodrug	A medication that is inactive until it is converted enzymatically to its active metabolite
Single nucleotide polymorphism (SNP)	A single base-pair change in a DNA sequence compared with the "common" or "wild-type" sequence
Variant allele	The allele at a particular SNP that is the least frequent in a population
Wild-type allele	The allele at a particular SNP that is most frequent in a population also called the "common" allele

From Attia J, Ioannidis JP, Thakkinstian A, et al. How to use an article about genetic association, A: background concepts. *JAMA*. 2009;301:74-81.

The Impact of Pharmacogenomics on Pain Medicine

In terms of efficacy, toxicity, pharmacokinetics, metabolism, and drug transport, differences in clinical response to pain medications have been linked in part to genetic variations.[4] To understand how pharmacogenomics can guide medication selection, it is important first to review how drugs are metabolized. Most medications are primarily metabolized in the liver. Hepatic metabolism occurs through phase I reactions, phase II reactions, or both. Phase I reactions are most commonly catalyzed by the cytochrome P450 (CYP450) system, whereas phase II conjugation enhances water solubility for excretion. The CYP450 genes encode enzymes responsible for the metabolism of approximately 75% of commonly prescribed medications.[14] CYP450 is classified by gene sequencing, assigned a family number, a subfamily letter, and then a number for the individual enzyme based upon the order in which it was discovered and is outlined in Figure 13.1.[15,16] Individual variations of CYP gene expression results in altered metabolism, impacting drug concentration and response. These CYP variations are dependent on the metabolizer phenotype.[17] Pharmacogenetic testing for variant and wild-type alleles of CYP450 enzyme groups patients by their phenotype. Poor metabolizers who have two nonfunctional enzyme alleles resulting in an inability to metabolize; intermediate metabolizers, who have at least one reduced functional allele of an enzyme; extensive metabolizers, who have at least one functional allele; and ultra-rapid metabolizers, who have multiple copies of a functional allele or an allele with a promoter mutation that confers increased transcription of that gene.[17,18] Extensive metabolizers, the typical phenotype, obtain the expected therapeutic benefit and adverse effect profile from standard doses of a drug. In contrast, individuals who are poor metabolizers are at risk of poor efficacy or adverse effects if given a prodrug that is incompletely metabolized because of genetic



• **Figure 13.1** Cytochrome P450 enzyme Tree. Adapted from Riddick DS, Drug biotransformation. In: Kalant H and Roschlau W (Eds.). *Principles of Medical Pharmacology.* 6th ed. New York: Oxford University Press: 1997. and reprinted with permission from paindr.com.

differences in their liver enzyme systems. For example, a patient who is a poor metabolizer may not be able to convert the parent drug of an opioid into the active metabolite needed for analgesia (i.e. codeine to morphine, tramadol to o-desmethyltramadol). In contrast, ultra-rapid metabolizers can be prone to adverse effects because of higher than expected drug concentrations from enhanced metabolism (i.e. morphine toxicity from rapid metabolism from codeine).[19]

Non-CYP Polymorphisms

Genetic determinants beyond metabolic enzymes (such as the CYP450 family) also affect an individual's response to opioid analgesics. These include drug transporters and drug targets such as the μ-opioid receptor gene OPRM1. A common polymorphism of OPRM1 is the substitution of a single nucleotide at position 118 with an adenine substitution by guanine. The reported allelic frequencies for this are estimated at 10% to 30% among Caucasians, lower among African Americans, and higher among Asians.

Polymorphism of the OPRM1 gene can result in reduced expression of μ-opioid receptors. There is great interest in this polymorphism because it has been associated with pharmacologic and physiologic consequences affecting not only experimental pain models but also neuraxial opioid use for labor analgesia, postoperative analgesia, and cancer-related pain.[20] Studies have suggested that patients presenting with this genetic polymorphism may require higher doses of opioids for analgesic benefit.[21] The different combinations of these single nucleotide polymorphisms (SNPs) within genes that code for the targets of opioid analgesics (e.g. OPRM1) may result in different clinical effects, and thus knowledge of these for a specific patient could one day allow for improved outcomes for opioid prescribing. In addition to the CYP450 family of enzymes, the μ-receptor gene (OPRM1, p.118A/G), and the catechol-O-methyltransferase (COMT Val158MET), several types of the adenosine triphosphate (ATP)-binding cassette, and subfamily B member one gene (ABCB1) have been extensively studied.[20]

Methylenetetrahydrofolate reductase (MTHFR) and COMT are crucial in opioid and anti-depressant response. Patients with chronic pain often present with comorbid mental health disorders. COMT enzyme regulates the breakdown of serotonin, dopamine, norepinephrine, and putative neurotransmitters, while MTHFR is responsible for converting 5,10-Methylenetetrahydrofolate to 5-Methyltetrahydrofolate to its active, usable form of folate. The COMT Val158MET polymorphism is associated with low COMT activity, resulting in increased concentrations of dopamine and norepinephrine.[22] High concentrations of dopamine are associated with upregulation of opioid receptor expression. Ultimately, patients with the Val158MET variant may require fewer opioids for pain relief. [20] MTHFR polymorphism is associated with folate bioavailability impairment.[22]

It has been determined that the interaction of several polymorphisms likely influences the pharmacokinetics and pharmacodynamics of medications—for example, inherited differences—in drug targets (receptors) and drug metabolism and drug transport.[20] Recognizing that morphine and most clinically used opioids act via the μ-opioid receptor, the concept of μ-receptor multiplicity has been studied with the recognition that different splice variants of the MOR-1 gene exist with the potential to clinically affect the benefits or lack thereof of morphine and other opioid analgesics.[23] This kind of information will likely affect the manner in which clinicians prescribe opioids in the future.

Research continues to demonstrate the necessity of genomic testing, as it can optimize medication efficacy, reduce adverse events, decrease hospitalizations, and even prevent deaths in select cases.[24] Additionally, studies have also concluded cost effectiveness on clinical outcomes when genotyping is performed.[25]

Tricyclic Anti-depressants

Consider the patient example described above, in which the tricyclic anti-depressant (TCA) administered to the patient presenting with PHN led to intolerable adverse effects. As previously mentioned, TCAs are one of the many medications metabolized in the liver by the CYP450 system, and polymorphisms within this class of enzymes can lead to reduced or accelerated metabolism of their substrates.[26] As such, two individuals having the same weight and given the same drug dosage can have more than a 1000-fold difference in their plasma drug levels.[4] This can be extremely important to recognize from a clinical viewpoint as the plasma drug concentrations in individuals given the same dose of anti-depressants have been found to vary—primarily based on the polymorphisms present in the CYP2D6 enzyme (and CYP1A2, CYP2C19, and CYP3A4/5).[27,28] Relevant to the patient presented at the beginning of this chapter, individuals who are poor metabolizers of TCAs (approximately 7% of the Caucasian population) tend to accumulate drug concentrations outside of the narrow therapeutic range of the drug classes, leading to adverse TCA effects at lower than expected doses.[18,26] In contrast, patients who are CYP2D6 ultra-rapid metabolizers may require higher doses to achieve analgesia.[18,27,28] Potentially, the patient presented is a CYP2D6 poor metabolizer.

The value of genotyping before prescribing anti-depressants was considered in a large population-based study of 1198 elderly Dutch patients. Perhaps not surprisingly, poor metabolizers of TCAs more than extensive metabolizers required either lower maintenance doses or discontinuation of TCAs altogether.[25] Although research does not provide clear evidence to support the routine clinical use of liver enzyme genotyping before analgesic treatment, an increasing number of commercial entities have developed the capabilities to perform these assays. Thus they are now available for the clinician to consider using.[4] Clinically, the recognition that an individual patient could be a poor metabolizer, with or without confirmatory testing, can assist the prescriber to consider medication changes (dose adjustment or frank discontinuation) when poor efficacy or adverse events are observed.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Pharmacogenomic research in pain management has identified wide interindividual variation in the analgesic efficacy of both nonspecific NSAIDs and selective inhibitors of cyclooxygenase-2 (COX-2) because of SNPs within the COX genes.[29,30] A SNP in the promoter for the gene encoding COX-2 (the -1195G to A change) has a prevalence of greater than 10% and has been associated with mild asthmatic reactions.[31] Indeed, another functional effect of the increased expression of COX-2 potentially mediated by several SNPs is the enhanced susceptibility to hypersensitivity in response to standard doses of aspirin and other NSAIDs that inhibit COX-2, otherwise known as aspirin-intolerant asthma.[32] Additionally, a large genotyping study has determined that individuals with specific variants of the COX-1 and COX-2 genes have an increased risk of cardiovascular disease when taking aspirin.[29] Other studies have investigated an association between genotypes of the cytochrome P450 enzyme CYP2C9 and taking NSAIDs metabolized by that enzyme. An increased risk of developing gastroduodenal bleeding was noted in patients with this co-occurrence.[33–35]

Opioid Analgesics

Single Nucleotide Polymorphisms

In properly selected patients, opioids can be effective treatments for acute and chronic moderate to severe pain.[36] Similar to tricyclic anti-depressants, most opioids are metabolized by the CYP450 enzyme class (Table 13.2).[18] Hence, SNPs in CYP450s can have an impact on clinical analgesia and adverse effect responses. In particular, codeine has been associated with variable individual clinical responses. Codeine itself does not have analgesic activity as it is a prodrug: a medication that is inactive until it is enzymatically converted to its active metabolite. Approximately 10% of codeine is converted to its active metabolite, morphine, via CYP2D6 to provide analgesia.[20] Therefore patients with an ultra-rapid phenotype are at increased risk of respiratory depression because of extensive conversion of morphine.[37] The rest of codeine is converted to inactive metabolites via CYP3A4 and glucuronidation.[20,37,38] In contrast, CYP2D6 poor metabolizers may experience suboptimal analgesic efficacy when prescribed "routine" doses of codeine. This is also true for tramadol, another prodrug that undergoes extensive metabolism to the active metabolite via 2D6, and utilization of 3A4 and 2B6 to inactive metabolites produce opioid receptor mediated analgesia.[37] Figure 13.2 outlines the metabolism of common opioids and substrates. Tramadol is metabolized to O, N-desmethyltramadol by CYP3A4 and the primary active metabolite o-desmethyltramadol (M1) by CYP2D6. Notably, tramadol provides analgesia not only through opioid meditated receptors but also through inhibition of norepinephrine reuptake, similar to anti-depressant's mechanism of action. However, the reuptake inhibition of serotonin by tramadol does not provide analgesia, although abrupt discontinuation could result in serotonin withdrawal, which is often misinterpreted as opioid withdrawal. This is particularly important when selecting an agent as the risk of serotonin toxicity is increased with concomitant use of serotonergic medications such as serotonin reuptake inhibitors (SSRIs) (i.e. fluoxetine, paroxetine, sertraline).[20,38,39]

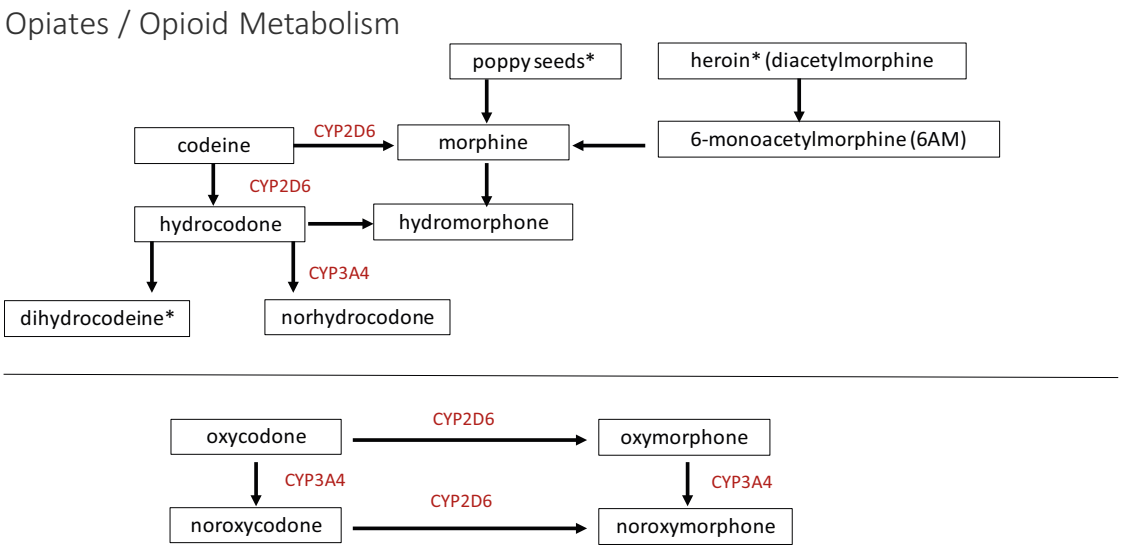
The extensive metabolism of tramadol (Fig. 13.3) also presents the opportunity for significant drug interactions, as when paired with an inhibitor of the CYP2D6 pathway, the expected response is similar to those with reduced CYP2D6 phenotype expression. An alternative option to consider in this case is the structurally similar tapentadol, which conversely, tapentadol avoids the CYP450 system, metabolized by phase II with no active metabolites. This makes tapentadol a lower risk medication for drug-drug CYP450 drug interactions and avoids the potential for genetic polymorphisms to impact metabolism. Unlike tramadol, tapentadol has a significant binding affinity for the μ-opioid receptor, and it has norepinephrine reuptake inhibiting properties only, with no effect on serotonin reuptake.[39]

The metabolism of many currently available opioids can be affected by SNPs with the CYP450 system; however, five opioid analgesic medications are not metabolized through this system at prescribed doses: hydromorphone, levorphanol, morphine, oxymorphone, and tapentadol.[37,40] Therefore if it has been identified, perhaps by noting poor analgesic efficacy or intolerable adverse effects (or even possibly actual pharmacogenetic testing) that an individual has an SNP that alters the enzymatic activity of one or more of the CYP450 isoenzymes; an opioid analgesic (if otherwise appropriate for that patient) might be considered that is not

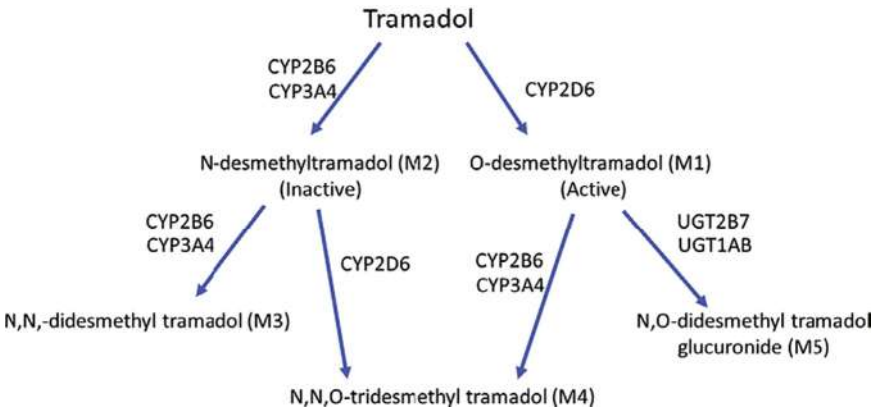
TABLE 13.2 Metabolizer Status by Racial/Ethnic Group

Gene or Enzyme	Examples of Drugs Metabolized by This Enzyme	Phenotype and Frequency by Groups	Clinical Effect
CYP1A2	Anti-convulsants: phenytoin, carbamazepine substrates Anti-depressants: clomipramine, fluoxetine, fluvoxamine, imipramine, maprotiline, nortriptyline Muscle relaxant: cyclobenzaprine NSAIDs: acetaminophen, naproxen	PM: Caucasian, 12%	Weak metabolism of enzyme
CYP2C9	Warfarin substrates Phenytoin Angiotensin II blockers: irbesartan, losartan NSAIDs: celecoxib, diclofenac, ibuprofen, meloxicam, naproxen Oral antidiabetics: glipizide, tolbutamide	PM: Caucasian, 2%-6%	Weak metabolism of enzyme
CYP2C19	Anti-convulsants: diazepam, phenytoin substrates Proton pump inhibitors: omeprazole, pantoprazole	PM: Caucasian, 2%-6%; Chinese,15%-17%; Japanese, 18%-23%	Weak metabolism of enzyme
CYP2D6	Analgesics: codeine, dextromethorphan, oxycodone, tramadol substrates Antiarrhythmic drugs: ajmaline, flecainide, mexiletine, propafenone Antiemetics: metoclopramide Antipsychotics + SSRIs: fluoxetine, haloperidol, paroxetine β-Blockers: metoprolol, propranolol, timolol 5-HT3 antagonists: ondansetron, tropisetron TCAs: amitriptyline, clomipramine, desipramine, imipramine	PM: Caucasian, 3%-10%; Chinese/Japanese/African American, <2% UR: Ethiopian, 20%; Hispanic, 7%; Scandinavian, 1.5%	Weak metabolism of enzyme Enhanced metabolism of enzyme substrates

5-HT3, serotonin; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PM*, poor metabolizer; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic anti-depressants; *UR*, ultra-rapid.
Adapted from Fishbain DA, Fishbain D, Lewis J, et al. Genetic testing for enzymes of drug metabolism: does it have clinical utility for pain medicine at the present time? A structured review. *Pain Med*. 2004;5:81-93; and Stamer UM, Stuber F. Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol*. 2007;20:478-484.



• **Figure 13.2** Shown in red are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary. Pharmacogenetic testing is available for CYP2D6 and CYP3A4. | Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most opioids. Reprinted with permission from paindr.com.



• **Figure 13.3** Tramadol Metabolism. Gong L, Stamer UM, Tzvetkov MV, Altman RB, Klein TE. PharmGKB summary: tramadol pathway. *Pharmacogenet Genomics*. 2014;24(7):374-380. Reprinted with permission from paindr.com. Available at: https://paindr.com/wp-content/uploads/2020/08/tramadol-metabolism.pdf.

metabolized through this mechanism to increase the likelihood of a successful treatment outcome.

The current clinical value of pharmacogenomic research illustrates that pharmacogenomic data may play a role in risk stratification and may help guide prescribers in their decision making. Relevant to the patient presented previously, 41% to 51% of individuals of Asian origin express an unstable CYP2D6 enzyme, whereas 12% to 21% of Caucasian people express an inactive CYP2D6 enzyme.[41] However, in clear contrast, 10% to 29% of people of Ethiopian or Saudi Arabian descent have heightened CYP2D6 activity.[41] When considered for the purposes of clinical decision making, this pharmacogenomic information can provide clues about how a specific patient may respond to codeine, and other opioids metabolized by CYP2D6 and, thereby, offer prescribing guidance (Table 13.3). The patient presented may be genetically predisposed to low CYP2D6 activity. His inherent enzymatic capacity may not be sufficient to obtain analgesia from the prodrug codeine and other opioids such as hydrocodone (hydrocodone is metabolized to hydromorphone through a CYP450-dependent process).[42] Pharmacogenomic information may provide the connection between the opioid prescribed and the lack of expected clinical response or the presence of unexpected adverse effects. Opioid responsiveness is widely recognized as a highly individualized phenomenon that depends on many factors, including pain etiology, prior exposure to opioids and opioid tolerance level, and other psychophysiological determinants. Consequently, pharmacogenomics can have a significant impact on the clinical response to opioid therapy.[43]

Alternative Splicing

Although most studies concerning opioid-response variability have focused on SNPs, other investigators are examining cellular mechanisms that may contribute to the interindividual variable response to opioid analgesics.[44] Evidence has identified multiple μ-opioid receptor subtypes, often referred to as "splice variants," with distinct properties that influence the pharmacodynamics of individual opioids.[44] To understand this source of diversity, consider a brief review of the central tenets of molecular biology.[10]

Genetic material (DNA) is transcribed into ribonucleic acid (RNA) and then translated into proteins, with cellular structural, enzymatic, and receptor functions. SNPs are sources of variation in the DNA, while diversity is also introduced during the transcription of RNA, during which alternative splice variants are produced. This idea was proposed in the 1980s by Nobel Prize winner Walter Gilbert and has since been well characterized and is recognized as the major source of proteome diversity enabling the complexity of human traits.[26]

Alternative splice variants of the μ-opioid receptor have been identified and correlated with the clinical phenomenon of incomplete cross-tolerance by which tolerance to one opioid does not translate to tolerance to other opioids.[23] In addition, although most clinically used opioids are selective for the μ-opioid receptor, their ability to activate the receptor can vary, leading to widely different efficacies and side effect profiles between individual patients. The minimal effective analgesic concentration for morphine can vary among patients by as much as 10-fold.[45] Further response variation within an individual is related to gene expression patterns changing over time and even diverging across organ systems and tissues, based on an individual's state of health and the degree or type of physiologic or emotional stress present.

As previously mentioned, clinically significant response variation in both the efficacy and adverse events of opioids and other analgesics has been noted for many years.[46a,46b] Chronic opioid therapy treatment guidelines developed by the American Pain Society and the American Academy of Pain Medicine recommended considering "opioid rotation" (e.g. switching from one opioid to another) if the initially prescribed opioid is neither well tolerated nor clinically effective after a reasonable trial.[36] Grilo and colleagues completed a study of patients with difficult-to-treat rheumatologic pain, in which most patients rotated from morphine to either transdermal fentanyl or hydromorphone.[46a,46b] Those patients who underwent opioid rotation experienced a mean reduction of 30 mm on a visual analog scale, indicating a clinically meaningful reduction in pain intensity.[46a,46b,47] In a study of opioids for the treatment of chronic non-cancer pain, Quang-Cantagrel and colleagues reported that the first long-acting opioid

TABLE 13.3 Enzymes Involved in Opioid Metabolism

Class	Drug	Metabolism
Phenanthrenes	Codeine	10% CYP3A4 (to norcodeine); 5% CYP2D6 (to morphine); 80% UGT2B7
	Hydrocodone	CYP2D6 (to hydromorphone) and CYP3A4 (to norhydrocodone); other minor non-CYP oxidative enzymes
	Morphine	UGTs (GYP-metabolized products)
	Oxycodone	Hepatic glucuronide by UGT1A3 and UGT2B7
		CYP2D6 (to oxymorphone) and CYP3A4 (to noroxycodone); GYP-metabolized product(s) by UGTs
	Dihydrocodeine	5%-10% CYP2D6 (to dihydromorphine) and CYP3A4 (to nordihydrocodeine); 85% UGT2B7
	Hydromorphone	Hepatic glucuronide conjugation via UGT1A3, UGT2B7; dihydromorphinone ketone reductase
	Oxymorphone	UGT1A3 and UGT2B7, with UGT2B7 being the predominant enzyme
	Buprenorphine	CYP3A4 (65%), CYP2C8 (30%), CYP3A5, CYP3A7,CYP2C9, CYP2C19, and CYP2C18; GYP-metabolized product(s) further cleared by UGTs
	Naloxone	Conjugation with glucuronic acid via UGTs, mainly UGT2B7
	Naltrexone	Aldo-keto reductase (dihydrodiol dehydrogenase); glucuronidation via UGTs
Diphenylheptylamine	Methadone	N-demethylation by CYP3A4
	Propoxyphene	N-demethylation by CYP3A4
Phenylpiperidines	Fentanyl	N-dealkylation by CYP3A4
	Meperidine	CYP3A4, CYP286, and CYP2C19
	Remifentanil	Nonspecific blood and tissue esterases to remifentanil acid
	Sufentanil	N-dealkylation by CYP3A4
Phenylpiperidine derivatives	Loperamide	N-demethylation by CYP2B6, CYP2C8, CYP2D6, and CYP3A4
Phenylpropylamine	Tramadol	O-demethylation by CYP2D6; N-demethylation by CYP286 and CYP3A4
	Tapentadol	N-demethylation (13%) by CYP2C9 and CYP2C19; Hydroxylation (2%) by CYP2D6; Hepatic glucuronide (55%) by UGT1A9 and UGT2B7

CYP, Cytochrome P450; *UGT*, uridine diphosphate glycosyltransferase.

From Kadiev E, Patel V, Rad P, et al. Role of pharmacogenetics in variable response to drugs: focus on opioids. *Expert Opin Drug Metab Toxicol*. 2008;4:77-91.

Fudin J. 2018. Chemical classes of opioids. Reprinted with permission from paindr.com. Available at: https://paindr.com/wp-content/uploads/2018/10/Opioid-Structural-Classes-Figure_-updated-2018Oct.pdf.

prescribed was effective for 36% of patients.[48] However, the initially prescribed opioid had to be discontinued because of adverse effects in 30% or ineffectiveness in 34% of those studied. Eventually, a clinical response was obtained by changing to a second (31% responded), third (40% of the remainder responded), fourth (56% of the remainder responded), and fifth (14% of the remainder responded) opioid.[48] These data, however, do not indicate that eventually, a patient will respond to a particular opioid, and thus it is important to note that the failure of one opioid does not predict the patient's response to another opioid analgesic.[49]

The concept of opioid rotation is based not only on empirical clinical observations but also on the pharmacogenetic considerations discussed earlier. Safe and effective opioid rotation requires specific clinical knowledge; if opioid rotation is believed to be an appropriate approach to managing the care of an individual patient, guidelines are available for the calculation of equianalgesic dosing and other important steps in this process.[43]

Future Outlook and Conclusions

Advances in pharmacogenomics continue to grow and allow clinicians to more precisely individualize optimal pharmacologic care for their patients with acute and chronic pain. Commercial pharmacogenomic testing is currently available. However, cost and provider education and result interpretations are still an obstacle to implementing its use as a standard of care. It is critical for prescribing clinicians to be trained and proficient in understanding the influence of genetic and genomic variations on drug responses or consider collaborating with a pharmacist with specialized training. The potential benefits of such testing are attractive enough, given the potential for more effective and safer management of patients with acute and chronic pain to warrant further study to improve their clinical applicability.

Key Points

- Pharmacogenomics is the study of the impact of genetics on pharmacotherapeutic responses and tolerability to improve drug safety and efficacy through genetically guided, individually tailored treatments.
- Advances in pharmacogenomics allow for a better understanding as to why patients may have variable responses to various analgesic therapies and may soon allow an opportunity for clinicians to identify the most appropriate pharmacotherapies for a patient *before* prescribing.
- SNPs in the CYP450 system can lead to drug response variability impacting drug efficacy and safety.
- Genetic variance can impact the therapeutic response of specific pain medications or predispose an individual to adverse effects.
- Extensive metabolizers obtain the expected therapeutic benefit from standard doses of a drug. In contrast, individuals who are poor metabolizers are at risk of poor efficacy and/or adverse effects if given a prodrug that is incompletely metabolized because of genetic differences in their liver enzyme systems.
- It is important to consider metabolite activity when determining the impact of genetic polymorphism on medication selection. A prodrug will have the opposite effect compared to a medication without active metabolites.

Suggested Readings

American Medical Association. Pharmacogenomics: Increasing the safety and effectiveness of drug therapy. 2011.

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Psychosocial and Psychiatric Aspects of Chronic Pain

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Introduction

When a patient presents to a healthcare provider with a symptom of pain, the initial focus is on the patient's medical history and the underlying pathology—a search to identify the "broken body part" that once identified is treated to eliminate the symptom. When pain is not easily alleviated and becomes chronic, it can cause a patient (provider and significant others) significant distress with many other ongoing difficulties that compromise all aspects of their lives. Living with chronic pain requires considerable emotional resilience as it depletes people's emotional reserves; the continuing quest for relief often remains elusive, leading to feelings of demoralization, helplessness, and hopelessness.

Historically, the amount of pain a person reported was expected to be related to the amount of tissue damage—"somatogenic." When the presence and extent of pain report was not adequately explained by any identifiable pathology, pain was considered "functional" or "psychogenic." Psychological factors were then considered to be playing a causal role. However, over the past four decades, research has consistently demonstrated that pain is not unidimensional; it is instead a complex biopsychosocial phenomenon. A range of cognitive, affective, behavioral, and sociocultural factors, in addition to physical and other biomedical factors, all contribute to the chronic pain experience. Treating individuals with chronic pain requires a comprehensive approach customized to each patient's unique characteristics and needs.

Advances in the knowledge of the neurophysiology of pain have resulted in the development and evolution of pharmacologic agents, surgical interventions, innovative technologies (e.g. spinal cord stimulation, implantable drug delivery systems), and nonpharmacologic treatments (e.g. neurofeedback, cognitive-behavioral therapy) for the treatment of patients with chronic pain.[1–3] However, despite these developments, the amount of pain reduction averages only about 35%, and fewer than 50% achieved this result.[4] Therefore many people with persistent pain shuttle from healthcare provider to healthcare provider, diagnostic test to diagnostic test, in a frustrating and prolonged quest to achieve relief. This experience of "medical limbo"—the presence of a painful condition that, in the absence of acceptable pathology, is either attributed to psychiatric causation or malingering on the one hand, or an undiagnosed but potentially progressive and untreatable disease on the other—is itself a source of significant and ongoing stress that can initiate high levels of emotional distress or aggravate a premorbid psychiatric condition.[5]

The person who has chronic pain resides in a complex world populated not only by them but also by their significant others, including family healthcare providers, employers, and third-party payers. Family members feel increasingly hopeless and distressed as medical costs, disability, and emotional suffering mount while available treatment options and income decline. Healthcare providers grow increasingly frustrated and ineffective and defeated as available treatment options are exhausted, while the pain condition remains a mystery and with no end in sight. Providers may come to question the veracity of their patients and their complaints. Employers, who are already resentful of growing worker's compensation benefits, pay higher costs while productivity declines because the employee frequently calls out sick or cannot perform at his or her usual level ("presenteeism"), often with coworkers having to pick up the slack. Third-party payers watch as healthcare expenditures soar with repeated diagnostic testing, often with inconclusive results. In time, the legitimacy of the individual's report of pain may be questioned since often a physical etiology fails to substantiate the cause of the symptoms.

People with chronic pain may feel that their healthcare providers, employers, and even family members are skeptical, blaming them when their condition fails to respond to treatment as expected. Some may suggest that the individual is complaining excessively in an attempt to obtain prescriptions for centrally acting and reinforcing medications (e.g. opioids, mood altering), receive attention, benefit financially (i.e. obtain disability compensation), avoid undesirable activities, or be relieved from onerous obligations (e.g. gainful employment, household chores). Others may suggest that the pain reported is not real, that they are feigning or exaggerating their symptoms, and it is "all in their head." Often, the ensuring result is an unfortunate, inappropriate, and detrimental adversarial relationship between patients, their healthcare providers and employees.

As a result of these attitudes, and in the absence of a cure or even substantial pain relief, individuals experiencing chronic pain may withdraw from contacts, lose their sources of income, alienate family, friends, and coworkers, and become more and more isolated, despondent, and depressed. They may become angry and frustrated as their bodies, the healthcare system, legal system, and their significant other have all let them down; they may feel they have even let themselves down as they relinquish their usual activities and responsibilities because of symptoms that are intractable,

yet often inscrutable when not directly observable or validated by objective pathologic findings. This emotional distress can be exacerbated by a variety of other factors, including fear of disease progression and their vulnerability to escalating sets of symptoms and disabilities, insufficient or maladaptive support systems, inadequate personal and material coping resources, treatment-induced (iatrogenic) complications, including overuse of potent drugs with significant adverse effects, disruption of usual activities and sleep disturbance, inability to work, financial difficulties, and prolonged litigation. Living with persistent pain conditions requires considerable emotional resilience and tends to deplete people's emotional reserves, taxing not only the individual sufferer but also the capacity of family, friends, coworkers, employers, and society to provide support.

Based on what we describe above about the plight of the person with chronic pain, two conclusions are obvious: (1) psychosocial and behavioral factors play a significant role in the experience, maintenance, and exacerbation of pain and potentially even the cause,[6] and (2) since some level of pain persists in the majority of people with chronic pain regardless of treatment, self-management is an important complement to biomedical approaches.[7] In this chapter, we will emphasize a set of important psychological constructs, including dispositional, cognitive, affective, behavioral, and contextual factors. We discuss them individually for ease of explication. However, it is important to note that although we will describe these separately, there is considerable overlap and interaction among them. We will conclude with a discussion of integrative models and treatments for people with chronic pain.

Historical Models

Biomedical Model of Chronic Pain

The traditional biomedical model of pain—which dates back to the ancient Greeks and was inculcated into medical thinking and practice by Descartes in the 17th century—assumes that people's symptoms result from a specific disease state represented by disordered anatomy and pathophysiology. The diagnosis is confirmed by data from objective tests of physical pathology and impairments, and medical interventions are specifically directed toward correcting the organic dysfunction and organic source of pathology.

Healthcare providers often undertake Herculean efforts (often at great expense to the patient or third-party payer) attempting to establish the specific link between objective indications of tissue pathology and the reported presence and severity of pain. The expectation is that once *the* physical cause has been identified, appropriate treatment will follow. Treatment will then focus on eliminating or blocking the putative cause(s) of the pain, chemically (e.g. oral medication, regional anesthesia, implantable drug delivery systems), surgically (e.g. laminectomy, spinal fusion), or physically (e.g. spinal cord stimulation, transcutaneous electrical nerve stimulation [TENS]) on the pain pathways.

Several perplexing features of chronic pain do not fit neatly within the traditional biomedical model, suggesting an isomorphic relationship between pathology and symptoms. For example, pain may be reported even in the absence of identified pathologic process. It is estimated that one-third to one-half of all visits to primary care physicians are prompted by symptoms for which no biomedical causes can be detected.[8] In up to 86% of the cases, the cause of back pain is unknown despite the performance of sophisticated imaging.[9] Conversely, imaging studies using computed tomography scans and magnetic resonance imaging (MRIs) have noted the presence of significant pathology in up to 35% of *asymptomatic* people.[10,11] Yet, they do not appear to experience any pain. Thus those who report severe pain with *no* identifiable pathology and those with demonstrable pathology may *not complain* of or even experience any pain. Moreover, the nature of patients' responses to treatment often has little to do with their objective physical condition.[12]

Several different psychological perspectives on chronic pain have evolved because of the multiple psychosocial factors involved in the onset and maintenance of chronic pain. Many of the psychological treatments for chronic pain are based on different psychological principles, which differ and complete from one another. Thus it is important to consider the varying perspectives.

Psychogenic Perspective of Chronic Pain

As often happens in medicine, when a biologic explanation for symptoms seems inadequate or is disproportionate to objective physical pathology, the pain reports are attributed to a psychological etiology and thus are "psychogenic." The psychogenic perspective is the opposite of the biomedical model. When a patient's report of pain occurs in the absence of demonstrable pathology, it may be viewed as a psychiatric diagnosis within the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-V):[13] Pain disorder associated with psychological factors or even a pain disorder associated with psychological factors *and* a general medical condition.

A psychodynamic perspective on chronic pain was first described systematically in the 1960s. During this time, people with pain were viewed as having compulsive and masochistic tendencies, inhibited aggressive needs, and feelings of guilt—"pain-prone personalities."[14] It was commonly held that people with pain had childhood histories fraught with emotional abuse, family dysfunction (e.g. parental quarrels, separation, divorce), illness or death of a parent, early responsibilities, and high orientation toward achievement.[15] Some current research has reported associations between chronic pain and childhood trauma, although the research is not consistent.[16] Based on the psychogenic perspective, assessment of persons with chronic pain is directed toward identifying the psychopathologic tendencies that instigate and maintain pain. It is assumed that reports of pain will cease once the psychogenic mechanisms are resolved. Treatment is geared toward helping patients gain "insight" into the underlying maladaptive psychological contributors.[16,17]

Although the psychogenic pain notion is ubiquitous, empirical evidence supporting it is scarce. A substantial number of chronic pain patients do not exhibit significant psychopathology. Moreover, studies suggest that in most cases, the emotional distress observed in these patients occurs in response to the persistence of pain and not as a causal agent[18,19] and may resolve once the pain is adequately treated.[20] Furthermore, insight-oriented psychotherapy has not been shown to be effective in reducing symptoms for the majority of patients with chronic pain.[21] Studies suggest that the emotional distress observed in patients with chronic pain more typically occurs in *response to* the persistence of pain and not as a causal agent,[22,23] and may resolve once the pain is adequately treated.[20] The psychogenic model has thus come under critical scrutiny and may be flawed in its view of chronic pain.[24]

Secondary Gain Perspective on Chronic Pain

The secondary gain (motivational) perspective is a variant of the psychogenic model frequently invoked within the legal system. From this perspective, reports of pain in the absence of or in excess

of physical pathology are attributed to the desire of the patient to obtain some benefit such as time off from undesirable activities, financial compensation, or acquisition of mood altering drugs—*secondary gains.* In contrast to the psychogenic model, in the secondary gain view, the assumption is that the patient is *consciously* attempting to acquire a desirable outcome. The complaint of pain in the absence of pathologic process, thus, is regarded as fraudulent.[25]

Behavioral Formulations

Pain is an unavoidable part of human life. No learning is required to activate nociceptive receptors. However, pain is a potent and salient experience. Beyond mere reflexive actions, people must learn to avoid, escape, modify, or cope with noxious sensations. Three major behavioral learning principles can help us understand the acquisition of adaptive versus dysfunctional responses associated with pain: classical (respondent) conditioning, operant conditioning, and observational (social) learning.

Classical (Pavlovian, Respondent) Conditioning

According to the classical (Pavlovian, respondent) conditioning model, if a painful stimulus is repeatedly paired with a neutral stimulus, the neutral stimulus will elicit a pain response. The influence of classical conditioning (i.e. the result of a stimulus followed by a response) can be observed in pain patients. Consider physical therapy, a mainstay of treatments for chronic pain patients, where treatment may evoke a conditioned fear response in patients. A patient who experienced pain after performing a treadmill exercise, based on the frequent pairing of exercise followed by pain, may become "conditioned" to experience a negative emotional response to the presence of the treadmill and any stimulus and any contextual cues associated with the nociceptive stimulus (e.g. physical therapist, gym). The negative emotional reaction may instigate muscle tensing, thereby exacerbating pain and further reinforcing and thereby strengthening the association between the stimulus and response (pain). People with chronic pain may avoid and attempt to escape from activities previously associated with pain onset or exacerbation.

Once a pain problem persists, fear of motor activities may become increasingly connected (i.e. conditioned), resulting in avoidance of activity in anticipation of avoidance of pain. Avoidance of pain is a powerful rationale for the reduction of activity, where muscle soreness associated with exercise functions as a justification for further avoidance. Thus although it may be useful to reduce movement in the acute pain stage, limitation of activities can be maintained not only by pain but also by *anticipatory* fear that has been acquired through the mechanism of classical conditioning. Thus cognitive processes may intervene with pure conditioning. The anticipation motivates a conscious decision to avoid or seek to escape from specific behaviors or stimuli.

In chronic pain, many activities that were initially neutral or even pleasurable may come to elicit or exacerbate pain. So they are experienced as aversive and actively avoided. Over time, a greater number of stimuli (e.g. activities) may be expected to elicit or exacerbate pain and will be avoided. This process is called *stimulus generalization.* Thus the anticipatory fear of pain and restriction of activity, and not just the actual nociception, may contribute to disability. Anticipatory fear also can elicit physiologic reactivity (e.g. increased muscle tension) that may aggravate pain. As a consequence, conditioning may directly increase nociceptive stimulation and, subsequently, the perception of pain.

The conviction that patients hold that they should remain inactive is challenging to modify, as long as activity-avoidance succeeds in preventing aggravation of pain. By contrast, repeatedly engaging in behavior—*exposure*—that produces progressively less pain than was predicted (corrective feedback) will be followed by reductions in anticipatory fear and anxiety associated with the activity.[26] Such transformations add support to the importance of a quota-based physical exercise program, with patients gradually and progressively increasing their activity levels despite fear of injury and discomfort associated with the use of deconditioned muscles.[27] This exposure, in the absence of anticipated pain, provides the *corrective feedback* that should be positively reinforcing and increase the likelihood of continuation of previously avoided activities.

Operant Conditioning

The effect of environmental factors in shaping the experience of people with pain was acknowledged long ago.[28] However, a new era in thinking about pain began with Fordyce's extension of *operant conditioning* to chronic pain.[29] The fundamental principle is that if the *consequence* of a given behavior is rewarding, its occurrence increases, whereas if the consequence is aversive, the likelihood of its occurrence decreases. The key in this model is the role of consequences. The main focus of operant learning is modification in the frequency of a given behavior—increasing desirable behaviors and extinction of maladaptive behaviors. When a person is exposed to a stimulus that causes tissue damage, the immediate behavioral response is withdrawal in an attempt to escape from noxious sensations. Such reflexive behaviors are adaptive and appropriate. However, in chronic pain, avoidance may be maladaptive as it may lead to reductions in strength, flexibility, and endurance, all of which contribute to increasing disability. The principles of learning suggest that through a process of learning, responses that receive positive consequences (positive reinforcement), especially repeated desirable consequences, will more likely be maintained; behaviors that fail to activate positive consequences, or that receive negative consequences (punishment), will be less likely to occur and thus reduced (i.e. extinguished) or avoided. Behaviors may also be maintained by the escape from undesirable events, in the case of pain, by the use of analgesic drugs, rest, or the avoidance of undesirable activities.

Fordyce underscored the fact that since there is no objective way to measure pain—no pain thermometer that can accurately measure the amount of pain a person feels or should be experiencing—the only way we can know of anyone's pain is by their behavior, whether verbal or nonverbal expressions labeled *pain behaviors.* The pain behavior originally elicited by organic factors caused by injury or disease may later occur, totally or in part, in response to reinforcing environmental events.

Although pain behaviors include verbal reports, paralinguistic vocalizations (sighs, moans), motor activity, facial expressions, body postures and gesturing (limping, rubbing a painful body part, grimacing), functional limitations (reclining for extensive periods, inactivity), and behaviors designed to reduce pain (taking medication, use of the healthcare system).

The central features of pain behaviors are that they are (1) sources of communication and (2) observable. Observable behaviors are capable of eliciting a response, and the consequences of behavior will influence subsequent behavior. According to Fordyce,[29] these pain behaviors can become subjected to the principles of operant conditioning. That is, since these behaviors are observable, they are capable of evoking responses, and it is the consequences following the behavior that are particularly important as they can serve to maintain or diminish the likelihood of the behavior recurring.

Pain behaviors may be positively reinforced directly (e.g. attention from a spouse or healthcare provider, monetary compensation, avoidance of undesirable activity). Pain behaviors may also

TABLE 14.1 Operant Schedules of Reinforcement

Schedule	Consequences	Probability of the Behavior Recurring
Positive Reinforcement	Reward the behavior	More likely
Negative Reinforcement	Prevent or withdraw aversive results	More likely
Punishment	Punish the behavior	Less likely
Neglect	Prevent or withdraw positive results	Less likely

be maintained by the escape from noxious stimulation through the use of drugs or rest or the avoidance of undesirable activities such as work. In addition, "well behaviors" (e.g. activity, working) may not be positively reinforcing, and the more rewarding pain behaviors may be maintained.

Table 14.1 summarizes basic operant principles of conditioning. The operant learning paradigm does not explain the etiology of pain or initiation of the behavior but rather focuses primarily on the maintenance of pain behaviors and deficiency in well behaviors. Adjustment of reinforcement schedules will likely modify the probability of recurrence of pain behaviors and well behaviors.

It is important not to make the mistake of viewing pain behaviors as being synonymous with *malingering*. Malingering involves the patient *consciously* and *purposely* faking a symptom such as pain for some gain, often financial (secondary gain). There is no suggestion of conscious deception in the case of pain behaviors but rather the unintended performance of pain behaviors resulting from environmental reinforcement contingencies. Contrary to the beliefs of many third-party payers, there is little support for the contention that outright faking of pain for financial gain is prevalent.[30]

There is some support for the operant model.[31–33] For example, Romano et al.[33] videotaped patients and spouses in a series of cooperative household activities and recorded patients' pain behaviors. Sequential analyses showed that spouses' solicitous responses were more to precede and follow pain behaviors in patients than pain-free controls. At least a subset of patients demonstrate high levels of pain behaviors and benefit from treatment targeting these behaviors.[34]

Observational (Social) Learning Processes

The *social (observational) learning perspective* emphasizes the point that behavior can be learned not only by actual reinforcement of an individual's behavior but also by observation of how others respond and the consequences following responses—*observational learning* and *modeling* processes. That is, people can acquire behavioral responses that were not previously in their repertoire by the observation of others, particularly others whom they view as similar to themselves. For example, a middle-aged man might learn what to expect by observing how other middle-aged men with similar medical problems are treated. This is a powerful way of learning, especially when the others being observed are judged to be similar to the observer.

Expectancies and actual behavioral responses to nociceptive stimulation are based, at least partially, on prior social learning history. The culturally acquired perception and interpretation of symptoms determine how people deal with disease states. The observation of others in pain is an event that captivates attention. This attention may have survival value, may help to avoid experiencing more pain, and may help to learn what to do about acute pain.

Observed *models* can influence the expression, localization, and methods of coping with pain.[35] Physiologic responses may even be conditioned during observation of others in pain.[36] Expectancies and actual behavioral responses to nociceptive stimulation are based, at least partially, on prior experience, either direct or from observation of others. This may contribute to the marked variability in response to objectively similar degrees of physical pathology observed.

Families and Family Systems Perspective

In *family systems* (and this could be expanded to significant others and not only traditional conceptualizations of nuclear families), the family is viewed as an interactional unit, and family members profoundly impact each other's emotions, thoughts, and behaviors. Thus the functioning of family members is interdependent, and family relationships are an important factor not only in psychological but also physical health.[37]

Recent studies have pointed to the insecure parental attachment as a risk factor for the development of chronic pain.[38] Individuals who grew up with an insecure parental attachment have been shown to experience more pain and disability than individuals with secure parental attachment.[39] It has been suggested that biologic factors (e.g. hypothalamic-pituitary-adrenal axis, sympathetic and central nervous system, immune statue) mediate the association between insecure parental attachment and chronic pain. The experience of chronic stress within the family has also been hypothesized to contribute to the development of chronic illness.[40] Specifically, chronic stress within the family may play an important role in the sympathetic nervous system and endocrine dysregulation often found in chronic pain patients.

A major tenet of the family systems perspective is that families influence the development and maintenance of chronic pain.[41] One important mechanism is based on operant theory.[33, 34] Expressions of acute pain (reporting pain, grimacing, avoidance of activity, and use of pain medication) because they are overt and observable may be reinforced through expressions of concern from family members. In support of this idea, investigators[34] have found that spousal attentiveness to expressions of pain was positively correlated with higher levels of reported pain, pain behavior frequency, and disability. However, social interaction may not always be viewed negatively and may be important in building intimacy, serving as positive support for a person with pain who is distressed.[42] Marital satisfaction has also been identified as an important mediator of disability associated with chronic pain.[43] Recent research has noted that partners rarely acknowledged patients' motive for seeking validation and were more likely to attribute negative motives (e.g. expressing anger) to a patient's pain behaviors, which may lead to their hostility toward patients.[44]

Pain does not take place in isolation but in a social context. Pain does not occur solely in people's bodies, nor does it occur solely in their brains, but, instead, it occurs in their lives. The emphasis on the role of significant others is important, as it reminds us that to successfully treat chronic pain patients requires that we not only assess and treat the patient but must also target significant others that can either impede or facilitate rehabilitation.[45]

Gate Control Model

Although not a psychological formulation itself, the *gate control model (GCM)*[46] was the first to popularize the importance of central, psychological factors in pain perception. Perhaps the most important contribution of the GCM is the way it changed thinking about pain perception. Melzack and Casey[47] differentiated three systems related to the processing of nociceptive stimulation—sensory-discriminative, motivational-affective, and cognitive-evaluative—all thought to contribute to the subjective experience of pain. Thus the GCM specifically includes psychological factors as an integral aspect of the pain experience. It emphasizes the central nervous system mechanisms and provides a physiologic basis for the role of psychological factors in chronic pain.

The GCM contradicts the notion that pain is *either* somatic *or* psychogenic. Instead, it postulates that both factors have potentiating and moderating effects. According to this model, both the central and peripheral nervous systems interact to contribute to the experience of pain. It is not only these physical factors that guide the brain's interpretation of painful stimuli that is at the center of this model; psychological factors (e.g. thoughts, beliefs, emotions) are also painful stimuli.

Prior to the Melzack and Wall[46] formulation of the GCM, psychological processes were largely dismissed as reactions to pain. Although the physiologic details of the GCM have been challenged,[48] it has had a substantial impact on basic research. It can be credited as a source of inspiration for diverse clinical applications to control or manage pain, including neurophysiologically based procedures (e.g. neural stimulation techniques from peripheral nerves and collateral processes in the dorsal columns of the spinal cord, pharmacologic advances, behavioral treatments, and those interventions that target modification of attentional and perceptual processes involved in the pain experience).

Cognitive-Behavioral Perspective

The *cognitive-behavioral perspective (CB)*, perhaps the most commonly accepted model for the psychological treatment of individuals with chronic pain,[49,50] incorporates many features of the classical conditioning, operant conditioning, and social learning models and a range of psychological variables described below. However, this perspective suggests that cognitive factors rather than conditioning factors alone play an important role. The model suggests that conditioned reactions are largely self-activated based on *learned expectations* rather than automatically evoked. It suggests that behaviors and emotions are influenced by interpretations of events, emphasizing how peoples' beliefs and attitudes interact with physical, affective, and behavioral factors. It proposes that conditioned reactions are largely activated by learned expectations rather than automatically evoked. In other words, it is the person's information processing that results in anticipatory anxiety and avoidance. Therefore the critical factor is that people learn to anticipate and predict events and to express appropriate reactions.[51]

From the CB perspective, people with pain are viewed as having negative expectations about their ability to control certain motor skills without pain. They tend to believe they have limited ability to exert any control over their pain. Such negative, maladaptive appraisals about the situation and personal efficacy may reinforce the experience of demoralization, inactivity, and overreaction to nociceptive stimulation. These cognitive appraisals and expectations are postulated as having an effect on behavior, leading to reduced efforts and activity, contributing to increased psychological distress (helplessness) and subsequent physical limitations. If one accepts that pain is a complex, subjective phenomenon uniquely experienced by each person, then knowledge about idiosyncratic beliefs, appraisals, and coping repertoires becomes critical for optimal treatment planning and accurately evaluating treatment outcomes.

People with chronic pain's beliefs, appraisals, and expectations about pain, their ability to cope, social supports, their disorder, the medicolegal system, the healthcare system, and their employers are all important because they may facilitate or disrupt the sense of control. These factors also influence patients' investment in treatment, acceptance of responsibility, perceptions of disability, adherence to treatment recommendations, support from significant others, expectancies for treatment, and acceptance of treatment rationale. Research has consistently demonstrated that patients' attitudes, beliefs, and expectancies about their plight, themselves, their coping resources, and the healthcare system affect reports of pain, activity, disability, and response to treatment.

Cognitive interpretations also affect how patients present symptoms to others, including healthcare providers. Overt communication of pain, suffering, and distress (pain behaviors) will enlist responses that may reinforce maladaptive behaviors and impressions about the seriousness, severity, and uncontrollability of pain. That is, complaining of pain may induce physicians to prescribe more potent medications, order additional diagnostic tests, and, in some cases, perform surgery. Significant others may express sympathy, excuse the person with chronic pain from responsibilities, and encourage passivity, fostering further physical deconditioning. It should be obvious that the CB perspective integrates the operant conditioning emphasis on external reinforcement and respondent view of conditioned avoidance within the framework of information processing.

People with persistent pain often have negative expectations about their ability and responsibility to exert any control over their pain. They often view themselves as helpless. Such negative, maladaptive appraisals about their condition, situation, and their personal efficacy in controlling their pain and problems associated with pain reinforce their experience of demoralization, inactivity, and overreaction to nociceptive stimulation. These cognitive appraisals are posited as having an effect on behavior, leading to reduced effort, reduced perseverance in the face of difficulty, reduced activity, and increased psychological distress.

The CB perspective on pain management focuses on making patients aware of the the effects of their thinking (beliefs, expectations) and providing the patient with techniques to gain a sense of control over the effects of pain on his or her life and modifying the affective, behavioral, cognitive, and sensory facets of the experience. Behavioral experiences help show individuals with chronic pain that they can, more than they assumed, increase their sense of personal competence. Cognitive techniques (e.g. self-monitoring to identify relationships among thoughts, mood, and behavior, distraction using imagery, and problem solving) help place affective, behavioral, cognitive, and sensory responses under the person's control.

The assumption is that long-term maintenance of behavioral changes will occur only if the person with pain has learned to attribute success to his or her own efforts. There are suggestions that these treatments can result in changes of beliefs about pain, coping style, reported pain severity, and direct behavior changes. Treatment that results in increases in perceived control over pain and decreased catastrophizing also results in decreases in pain severity and functional disability. When successful rehabilitation occurs, there is a major shift from beliefs about helplessness and passivity

to resourcefulness and ability to function regardless of pain and from an illness conviction to a rehabilitation conviction.

Several studies have attempted to identify specific cognitive factors that contribute to pain and disability.[51–53] These studies have consistently demonstrated that a person's attitudes, beliefs, and expectancies about their plight, themselves, their coping resources, and the healthcare system affect reports of pain, activity, disability, and response to treatment. For example, people respond to medical conditions in part based on their subjective ideas about illness and their symptoms. When pain is interpreted as signifying ongoing tissue damage or a progressive disease, it is likely to produce considerably more suffering and behavioral dysfunction than if it is viewed as being the result of a stable problem that is expected to improve.

Healthcare providers working with chronic pain patients are aware that patients having similar pain histories and reports of pain may differ greatly in their beliefs about their pain. Behavior and emotions are influenced by interpretations of events and expectations rather than solely by objective characteristics of the event itself.

People develop fairly elaborate views of their physical states, and these views or representations provide the basis for action plans and coping. Beliefs about the meaning of pain and their ability to function despite discomfort are important aspects of expectations about pain. A good example of this is how chronic pain patients often demonstrate poor behavioral persistence in exercise tasks. Their performance on these tasks may be independent of physical exertion or actual self-reports of pain but rather be related to previous pain reports or anticipation and fear of injury, re-injury, or exacerbation of their pain.[26] These people appear to have a negative view of their abilities and expect increased pain if they performed physical exercises. Thus the rationale for their avoidance of exercise was not the presence of pain but their learned expectation of heightened pain and accompanying physical arousal that might exacerbate pain and reinforce patients' beliefs regarding the pervasiveness of their disability. If people view disability as a necessary reaction to their pain, that activity is dangerous, and that pain is an acceptable excuse for neglecting their responsibilities, they are likely to experience greater disability. These negative perceptions of their capabilities for physical performance form a vicious circle, with the failure to perform activities reinforcing the perception of helplessness and incapacity. Once again, we can see how behavioral (conditioning) factors interact with cognitive processes.

Certain beliefs may lead to maladaptive coping, increased distress, and greater disability. People who believe their pain will persist may be passive in their coping and fail to use strategies to cope with pain. People who consider their pain to be an unexplainable mystery may negatively evaluate their own abilities to control or decrease pain and are less likely to rate their coping strategies as effective in controlling and decreasing pain.[54] People's beliefs, appraisals, and expectancies regarding the consequences of an event and their ability to cope and adapt to their symptoms and changed life circumstances are hypothesized to affect functioning in two ways. They may have a direct influence on physiologic arousal and mood and an indirect one through their effects on coping efforts.[55]

Once beliefs and expectancies are formed, they become stable and rigid, and relatively impervious to modification. Individuals with chronic pain tend to avoid experiences that could invalidate their beliefs (disconfirmations) and guide their behavior in accordance with these beliefs, even in situations where these beliefs are no longer valid. As noted, they do not obtain corrective feedback. Thus people with chronic pain need to develop adaptive beliefs about the relationships among impairment, pain, suffering, and disability and de-emphasize the role of experienced pain in their regulation of functioning. Results from numerous treatment outcome studies have shown that changes in pain level do not parallel changes in other variables of interest, including activity level, medication use, return to work, rated ability to cope with pain, and pursuit of further treatment. If healthcare providers hope to achieve better outcomes and reduce their frustration from patients' lack of adherence to their advice, they need to learn about and address patients' concerns within this therapeutic context.

The biomedical, psychogenic, secondary gain, and behavioral views described are unidimensional. Reports of pain are ascribed to *either* physical *or* psychological factors. Rather than being categorical, either somatogenic or psychogenic, as suggested by the GCM, both physical and psychological components may interact to create and influence the perception and experience of pain.

Any physical abnormalities that are identified may be moderated by coexisting psychosocial influences. The complexity of pain is especially evident when pain persists over time as a range of psychological, social, and economic factors interact with physical pathology to modulate individuals' reports of pain and the impact of pain on their lives. In the case of chronic pain, healthcare providers need to search not only for the physical source of the pain through examination and diagnostic tests but also examine the patient's mood, fears, expectancies, coping efforts, resources, responses of significant others, and the impact of pain on the patients' lives (see Chapter 15 for measures to assess these cognitive factors).

Although in the majority of cases, biomedical factors appear to instigate the initial report of pain. Over time psychosocial and behavioral factors may serve to maintain and exacerbate the level of pain, influence adjustment, and contribute to excessive disability. Following from this view, pain that persists over time should not be viewed as solely physical or solely psychological; the experience of pain is maintained by an interdependent set of biomedical, psychosocial, behavioral, and contextual factors.[56,57]

People with chronic pain frequently terminate active efforts to manage pain and, instead, turn to passive coping strategies such as inactivity, medication, or alcohol to reduce pain and emotional distress. They also absolve themselves of personal responsibility for managing their pain and, instead, rely on family and healthcare providers. The thinking of chronic pain patients has repeatedly been shown to contribute to the exacerbation, attenuation, and maintenance of pain, pain behaviors, affective distress, adjustment to chronic pain, health care seeking, response to treatment, and disability.[58–61]

Biopsychosocial, Contextual Model

Although Melzack and Wall's GCM described previously introduced the role of psychological factors in the maintenance of pain symptoms, it focused primarily on the basic anatomy and neurophysiology of pain. The biopsychosoci, contextual model, which expands the CB model of pain, views illness as a dynamic and reciprocal interaction between biological, psychological, sociocultural, and contextual variables that shape the person's response to pain.[56,57,62] From this perspective, diversity in illness expression (which includes its severity, duration, and consequences for the individual) is accounted for by the interrelationships among biologic changes, psychological status, and the social and cultural contexts. All of these variables shape the person's perception and response to illness.

According to the biopsychosocial view of pain, pain experience results from a complex web of interaction among nervous and

physiologic systems (central and peripheral), psychological factors, and social variables.[56,63] For example, biologic factors may initiate, maintain, and modulate physical perturbations while psychological variables influence appraisals and perception of internal physiologic signs; social factors shape patients' behavioral responses to the perceptions of their physical perturbations. Conversely, psychological factors may influence biology by affecting hormone production,[64] brain structure and processes,[65] and the autonomic nervous system.[66] However, the picture is not complete unless we consider the direct effects of disease factors and treatment upon cognitive and behavioral factors. Biologic influences and medications (e.g. steroids, opioids) may affect the ability to concentrate, cause fatigue, and modulate peoples' interpretation of their state and of their ability to engage in certain activities.

At different points during the evolution of a disease or impairment, the relative weighting of physical, psychological, and social factors may change. For example, during the acute phase of a disease, biologic factors may predominate, but over time psychological and social factors may assume a disproportionate role in accounting for symptoms and disability. There is considerable variability in behavioral and psychological manifestations of dysfunction, both across persons with comparable symptoms and within the same person over time.

To understand the variable responses of people to chronic conditions, biologic, psychological, and social factors must be considered. A longitudinal perspective is essential. A cross-sectional approach will only permit consideration of these factors at a specific point, and chronic conditions continually evolve. At any one point in time, what is observed is a person's adaptation to interacting biologic, personal, and environmental factors. The hallmarks of the biopsychosocial perspective are (1) integrated action, (2) reciprocal determinism, and (3) development and evolution. No single factor in isolation—pathophysiologic, psychological, or social—will adequately explain chronic pain status. This can be contrasted with the traditional biomedical model, whose emphasis on the somatogenic-psychogenic dichotomy is too narrow in scope to accommodate the complexity of chronic pain.

From an integrative biopsychosocial perspective, pain is viewed as a subjective perception that results from the transduction, transmission, and modulation of sensory input filtered through a person's genetic composition and prior learning history and modulated further by their current physiologic state, idiosyncratic appraisals, expectations, present mood state, and sociocultural environment.

What is unique about the biopsychosocial model is that it considers the influence of higher order cognitions, including perception and appraisal and the environmental context in which these appraisals take place. It accepts that people are active processors of information and that behavior, emotions, and even physiology are influenced by interpretations of events rather than solely by physiologic factors.[56,62] Therefore people with chronic pain may have negative expectations about their own ability and responsibility to exert any control over their pain. Behaviors of people with pain elicit responses from significant others that can reinforce both adaptive and maladaptive modes of thinking, feeling, and behaving.

Loeser[67] originally formulated a general model that delineated four dimensions associated with the concept of pain: 1) nociception, the stimulation of nerves that convey information about possible tissue damage to the brain; 2) pain, the subjective perception that results from transduction, transmission, and modulation of sensory information; 3) suffering, the emotional responses triggered by nociception or some other aversive event associated with it, such as fear or depression; and 4) pain behavior, those things that people do when they are suffering or in pain, such as avoiding activities or exercise for fear of (re)injury. Then Waddell[68] emphasized that pain cannot be comprehensively evaluated without an understanding of the individual who is exposed to the nociception. Waddell also made a comparison between Loeser's[67] model of pain and the call by Engel[14] for a new, more biopsychosocial model in medicine. Engel proposed the important dimensions of the physical problem, distress, illness behavior, and the sick role, which corresponded to Loeser's dimensions of nociception, pain, suffering, and pain behavior, respectively. Thus with this general perspective, a diversity of pain or illness can be expected (including its severity, duration, and psychosocial consequences). To fully understand a person's perception and response to pain and illness, the interrelationships among biologic changes, psychological status, and the sociocultural context all need to be considered. Any model that focuses on only one of these dimensions will be incomplete.

Cognitive Factors: Predispositions, Appraisals, Beliefs, Perceived Control, and Self-Efficacy

Predispositions

Preexisting temperament and personality may show continuity and predispose individuals toward misinterpretation of pain sensations and maladaptive pain beliefs, or they can have a protective role contributing to resilience in the face of adversity.

Among the potential vulnerability factors that have been proposed are negative affectivity, anxiety sensitivity, and illness and injury sensitivity. *Negative affectivity* (NA), the tendency to experience negative emotional states in daily life,[69] may be considered as heritable, stable, and promoting a tendency to experience a broad range of negative emotions and to view the world as threatening and distressing.[70] NA has been associated with heightened vigilance to bodily sensations, symptom reporting, and interpretational biases toward ambiguous internal signals.[71–73] Studies in nonclinical populations have reported NA to predict lower pain tolerance.[74] While recent studies have suggested that NA is associated with greater pain intensity and functional impairment,[75,76] studies in chronic pain populations have so far not provided consistent evidence for a role of trait NA. Thus although NA has often been implicated as a vulnerability factor in chronic pain, convincing evidence is lacking.

More convincing has been the research on another potential vulnerability factor: *anxiety sensitivity* (AS). AS is defined as the fear of anxiety-related sensations and is conceived as a partly heritable personality trait.[77] Individuals with high AS interpret unpleasant physical sensations (such as rapid heart beating, feeling faint) more often as a sign of danger than individuals with low AS. There is growing evidence that AS may also be a risk factor for the maintenance and exacerbation of chronic pain and disability.[78] AS has been shown to correlate with measures of fear avoidance (described below) and is associated with distress, analgesic use, and impairment of physical and social functioning in patients across a wide range of different pain-related conditions.[79,80] Moreover, path analyses and mediation models suggest that AS exacerbates fear avoidance beliefs and the negative interpretation of bodily sensations, which in turn leads to enhanced pain experience and pain avoidance.[80–82]

In contrast to the extensive search after negative predisposing factors described, there has been relatively little research on protective factors for chronic pain and disability. Traditionally, research on resilience has focused on adaptive responses in the wake of significant adversity or challenge (e.g. developmental resilience, posttraumatic growth). In the context of pain, resilience might mean effective recovery from an injury, infection, or

other painful experience, both from a physical and psychosocial standpoint (e.g. effective resilience in the wake of an injury might ideally mean total resolution of pain and resumption of normal functioning). However, in patients for whom resolution of pain is unlikely, behavioral and cognitive responses to pain may have very different implications in terms of their adaptiveness. When a new and unfamiliar painful condition develops, a fearful and avoidant response may be protective; consistent with an evolutionary view of pain, new painful sensations may signal significant danger to the organism, such that mobilization of individual resources to escape pain and threat may prolong survival. However, prolongation of this fearful avoidant response tends to yield fewer benefits in cases of chronic pain and, instead, increases the risk of protracted physical disability, deconditioning, and psychosocial dysfunction.[83–86]

Several investigators[86,87] have proposed a model of resilience in chronic pain that follows a "temporal" order of adaptation, manifesting in three interrelated factors: *sustainability*, or prolonged and positive functioning despite the immediate presence of pain; *recovery*, or expedient and effective recovery from the negative consequences of pain; and *growth*, or long-term learning or personal development that may result in new strengths, protective attitudes, or skills because of chronic pain.

Three potential resilience factors are particularly relevant in chronic pain: optimism, hope, and psychological flexibility. A review of the literature suggests that optimism may be one of the most important personality traits in relation to adjustment to chronic pain. Dispositional optimism is defined as "the tendency to believe that one will generally experience good outcomes in life" and is distinguishable from neuroticism and trait anxiety.[88] In cross-sectional and prospective studies, optimism was found to be associated with better general health, adaptation to chronic disease, and recovery after various surgical procedures.[89–91]

Only a few studies have explored the role of dispositional optimism or hope in adaptation to chronic pain. For example, Buckingham and Richardson[92] found that dispositional optimism and psychological grit enhance the effect of resilience on pain threshold in moderation models. In studying rheumatoid arthritis patients, Treharne and colleagues[93] found that optimism was associated with less depression and pain and higher life satisfaction for patients in the early and intermediate stages of disease.

The primary mechanism of the beneficial effect of optimism may be differences in coping behavior between optimistic and pessimistic people.[94] In general, pessimists turn to avoidant coping strategies and denial more often, while optimists employ more problem-focused coping strategies. When problem-focused coping is not possible, they turn to coping strategies such as acceptance, use of humor, and positive reframing of the situation.[88] Thus it may not be the use of specific coping strategies, but the flexibility of coping that protects against disability and distress.[88] Snyder has described a similar pathway for hope, with people with low hope showing a tendency to catastrophize, whereas people with high hope seek means to encounter future challenges and show flexibility in finding alternative life goals when their original goals are blocked.[95] Psychological flexibility manifests as an ability to effectively and flexibly adjust behavioral efforts at goal-pursuit in a way that is consistent with one's values[96] despite the presence of pain and associated problems.

Individuals with chronic pain who better sustain their optimism, hope, and flexibility appear to be more able to persist in painful behavioral tasks,[97] and to be less susceptible to other pain-related difficulties, such as fatigue[98] and problematic opioid use.[99] Similarly, positive emotional states have been found to be predictors of better social,[100, 101] and physical functioning in some individuals with chronic pain.

Appraisal and Beliefs

Specific appraisal and beliefs are largely shaped by an individual's learning history through direct experience, observational learning, or information acquired from others. These experiences may interact with an individual's enduring traits, sociocultural background, prior learning and experiences, and the current context in which they reside. Personality factors may predispose some people to make certain kinds of appraisals and be more susceptible to some idiosyncratic beliefs than others.

Pain appraisal refers specifically to the meaning ascribed to pain by each individual.[102] In accordance with the transactional stress model,[103] a distinction can be made between a primary appraisal (evaluation of the significance of pain in terms of threatening, benign, or irrelevant) and secondary appraisal (evaluation of the controllability of pain and one's coping resources). Beliefs refer to assumptions about reality that shape how one interprets events and can thus be considered as determinants of appraisal. Pain beliefs develop throughout the lifetime because of an individual's learning history and cover all aspects of the pain experience (e.g. the causes of pain, its prognosis, appropriate treatments).

Appraisal and beliefs about pain can have a strong impact on an individual's response to pain. If a pain signal is interpreted as harmful (threat), it may be perceived as more intense, more unpleasant, and evoke more escape or avoidance behavior. For instance, Smith and colleagues[104] demonstrated that cancer patients who attributed pain sensations after physiotherapy directly to cancer reported more intense pain than patients who attributed this pain to other causes.

Pain appraisal and pain beliefs are also prominent determinants of adjustment to chronic pain.[102] Pain that is viewed as a signal of damage, leads to disability, is uncontrollable, and is a permanent condition has been shown to affect individuals' responses,[61,105] and these beliefs are widespread.[106,107]

Catastrophizing and Fear Avoidance Beliefs

Pain catastrophizing (note that people experiencing chronic pain hate this term as they view it as pejorative[108]) can be defined as an exaggerated, negative cognitive and emotional orientation toward actual or anticipated pain experiences. It is a cognitive process whereby one assumes the worst possible outcomes and interprets even minor problems as major calamities. For example, a patient with chronic pain might interpret a brief painful episode as a symptom of a serious underlying health problem.

A large volume of evidence suggests that catastrophizing about pain plays a significant role in defining the actual experience of pain. Pain-related catastrophizing thought patterns are fairly common in both acute and chronic pain; it has been associated with increased perceptions of both acute,[105,109] and chronic[110] pain severity and disability among groups with diverse pain diagnoses,[111–113] and is a significant predictor of pain-related functional disability.[114,115] Several studies have shown that inter-disciplinary pain rehabilitation programs, cognitive therapy, and mindfulness based interventions focused on reducing catastrophizing were related to significant reductions in pain intensity, disability, pain interference, medication usage, and maintenance of treatment benefits.[116–118]

Imaging studies may offer some explanations as to how catastrophizing influences pain perception. Catastrophizing appears to be

associated with specific brain regions.[119,120] For example, Seminowicz and Davis[120] examined functional MRI (fMRI) while pain-free subjects underwent laboratory pain testing. They found that the effect of catastrophizing on neural response to painful stimulation may depend on stimulus intensity levels. The neural response to mild pain was seen in regions representing attention, vigilance, and emotion. In contrast, the relationship was reversed with moderate pain level; this suggests that catastrophizing attenuates the descending inhibitory system to more intense stimuli, making it more difficult to disengage from pain. Similar results have been reported in an imaging study of fibromyalgia patients in which catastrophizing was related to the activation in the brain areas reflecting the attentional, anticipatory, and emotional activities in response to pain.[119] These studies suggest that catastrophizing adversely impacts pain experience through increased attention and negative anticipation of pain. Still other studies[94,121] used the diffuse noxious inhibitory control/conditioned pain modulation (DNIC/CPM) paradigm, demonstrating that catastrophizing may influence the pain modulatory process in pain-free individuals and predict pain following surgery.[122] Catastrophizing has also been associated with immune function (i.e. interleukin-6) responses to acute pain,[123] and stress hormones in response to laboratory-induced pain in individuals with chronic pain and pain-free individuals.[124]

Fear avoidance occurs when people with chronic pain anticipate that certain activities will increase their pain or induce further injury. These fears may contribute to the avoidance of activity and subsequently greater physical deconditioning, emotional distress, and, ultimately, greater disability.[125] Their failure to engage in activities prevents them from obtaining any corrective feedback about the associations among activity, pain, and injury.

Besides fear of movement, people with persistent pain may be anxious about the meaning of their symptoms for the future—will their pain increase, will their physical capacity diminish, will they have progressive disability where they ultimately end up in a wheelchair or bedridden? In addition to these sources of fear, people experiencing persistent pain may fear that on the one hand, people will not believe that they are suffering, and on the other, they may be told that they are beyond help and will "just have to learn to live with it." Such fears can contribute to additional emotional distress and to increased muscle tension and physiologic arousal that may directly exacerbate and maintain pain.

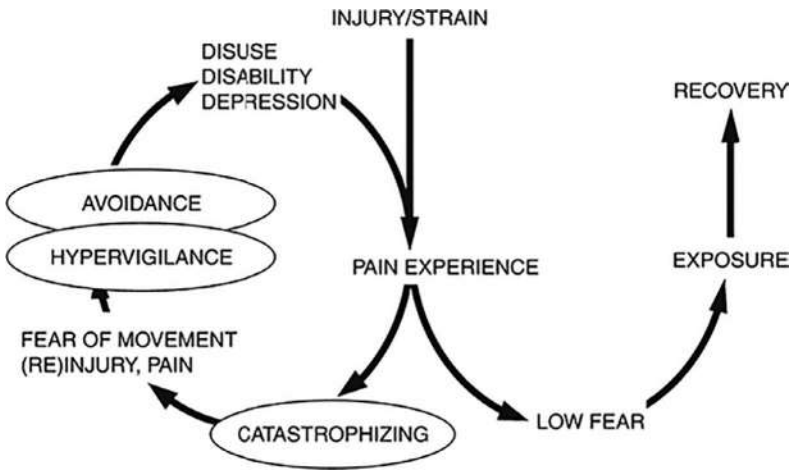
The role of catastrophizing and the belief that pain means harm and activity should be avoided has been most articulated in fear-avoidance models (FAMs) of chronic pain.[125,126] Although FAMs are multifaceted and include affective (fear) and behavioral (avoidance) components, cognitions are identified as the core determinants of entering into a negative pain cycle. The tenets of contemporary FAMs are depicted in Figure 14.1 and can be summarized as follows: When pain is perceived following injury, an individual's idiosyncratic beliefs will determine the extent to which pain is catastrophically interpreted. A catastrophic interpretation of pain gives rise to physiologic (arousal), behavioral (avoidance), and cognitive fear responses. The cognitive shift that takes place during fear enhances threat perception (e.g. by narrowing of attention) and further feeds the catastrophic appraisal of pain.[78,127]

There is substantial evidence that fear-avoidance beliefs are associated with disability and impaired physical performance in chronic pain.[126–128] A systematic review of the literature on psychological risk factors in back and neck pain indicated that the evidence for the association between fear-avoidance beliefs and increased pain and disability was of the highest level.[127,128] In addition, prospective studies have shown that fear-avoidance beliefs in patients seeking care for acute pain may be predictive of pain persistence, disability, and long-term sick leave.[129–131] Several treatment approaches have been developed and implemented to address pain-related fear and anxiety in chronic pain patients.[132]

Healthcare providers are not immune to fear-avoidance beliefs. Fear-avoidance beliefs of healthcare providers have also been found to be related to their treatment behavior and their recommendation for engaging in physical activities.[133,134] The beliefs of patients and healthcare providers may further interact with each other in a mutually reinforcing way because a patient's beliefs may guide the choice of which health care provider is visited.[135]

Perceived Control

Perceived control over pain refers to the belief that one can exert influence on the duration, frequency, intensity, or unpleasantness of pain. Perceived controllability of a pain stimulus may modify the meaning of this stimulus and directly affect threat appraisal.[136] As a consequence, pain may be rated as less intense or less unpleasant, and pain tolerance may increase.



• **Figure 14.1** Fear Avoidance Model. Reproduced with permission from Vlaeyen JW, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain.* 2012;153(6):1144-1147.

How people conceptualize their ability to control pain and associated stress seems to be an important determinant for how they cope with pain. Indeed, an increased sense of control has been shown to be linearly related to greater functionality in chronic pain patients.[61] Furthermore, improvement in control beliefs following inter-disciplinary pain treatment typically results in reduced pain and disability, perhaps because perceived control over the effects of pain has been shown to be more strongly related to better adjustment and less disability than perceived control over the pain itself.[61,137–139] The opposite end of the control spectrum is a sense of lack of control—helplessness. The literature generally supports that helplessness is associated with greater pain and poorer physical and psychological adjustment in chronic pain.[140]

Self-Efficacy

Related to perceived *control* is the construct of *self-efficacy* (SE). A SE belief is defined as a personal conviction that one can successfully execute a course of action (perform required behaviors) to produce the desired outcome in a given situation.[141]

SE is the conviction that one can successfully perform a certain task or produce a desirable outcome.[141] Given sufficient motivation to engage in a behavior, it is a person's SE beliefs that determine the choice of activities that he or she will initiate, the amount of effort that will be expended, and how long the individual will persist in the face of obstacles and aversive experiences. In this way, SE plays an important role in therapeutic change and compliance to psychological and medical regimes.[52]

SE judgments are based on four sources of information regarding one's capabilities, listed in descending order of importance:[141] one's own past performance at the task or similar tasks, the performance accomplishments of others who are perceived to be similar to oneself, verbal persuasion by others that one is capable, and perception of one's own state of physiologic arousal, which is, in turn, partly determined by prior efficacy estimation. Performance mastery can then be created by encouraging people to undertake subtasks that are initially attainable but become increasingly difficult and subsequently approaching the desired level of performance. It is important to remember that coping behaviors are influenced by the person's beliefs that the demands of a situation do not exceed their coping resources.

Recent reviews of psychological factors in chronic pain have concluded that the evidence for the role of SE across a broad range of pain populations is impressive.[142] Moreover, SE also influences the prognosis after acute physical interventions like surgery.[143] Prospective studies in patients who underwent surgery demonstrated that high SE before the start of rehabilitation and larger increases over the course of rehabilitation speed recovery and predict better long-term outcome.[144,145] Perceived SE has been shown to have a direct effect on the body's opioid and immune systems[146] confirming the important association between psychological constructs and physiology.

SE beliefs also play a role in the clinical presentation of chronic pain. Lower SE is consistently related to greater clinical pain ratings in various chronic pain conditions.[147–149] Low levels of SE beliefs are related to disability.[150,151] As was the case with a sense of control, SE beliefs mediate the relationship between pain and psychological functioning[152,153] in chronic pain. Furthermore, recent longitudinal studies suggest that poor SE beliefs are a risk factor for the development of functional disability associated with chronic pain[154] and work absenteeism.[155]

Whereas low SE beliefs are related to greater pain and dysfunction, improvement in SE is one of the best predictors for successful rehabilitation for pain patients. An elevated level of SE beliefs at pretreatment tends to predict better outcomes.[156,157] Furthermore, successful outcomes of pain therapy typically show associated improvement in SE, along with the improvement in depression and anxiety.[140,158–160]

Coping

Self-regulation of pain and its impact depends on people's specific ways of dealing with pain, adjusting to pain, and reducing or minimizing distress caused by pain; in other words, their coping strategies.[161] *Coping* is assumed to involve spontaneously employed purposeful and intentional acts, and it can be assessed in terms of overt and covert behaviors. Overt behavioral coping strategies include rest, use of relaxation techniques, or medication. Covert coping strategies include various means of distracting oneself from pain, reassuring oneself that the pain will diminish, seeking information, and problem solving. Coping strategies are thought to act to alter both the perception of pain intensity and the ability to manage or tolerate pain and to continue everyday activities.[7,56]

Some studies have found active coping strategies (efforts to function despite pain or to distract oneself from pain, such as engaging in an activity or ignoring pain) to be associated with adaptive functioning and passive coping strategies (such as depending on others for help in pain control and restricting one's activities) to be related to greater pain and depression.[151,162,163] However, beyond this, there is no evidence supporting the greater effectiveness of any one active coping strategy than any other. It seems more likely that different strategies will be more effective than others for some people at some times, but not necessarily for all people all the time.[164] This observation supports the importance of flexibility.

Several studies have been demonstrated that if patients are instructed in the use of adaptive coping strategies, their rating of the intensity of pain decreases and tolerance of pain increases.[165] More recently, some interventions have begun to incorporate smartphone apps to provide psychoeducation and coping strategies using an interactive platform and have found some efficacy using this approach.[166,167] Nevertheless, the most important factor in poor coping appears to be the presence of catastrophic thinking, not the nature of specific adaptive coping strategies.[168]

Emotion

Pain is ultimately a subjective, private experience, but it is invariably described in terms of sensory and affective properties. As defined by the revised definition, the International Association for the Study of Pain states that pain is "An unpleasant sensory and *emotional experience* associated with, or resembling that associated with, actual or potential tissue damage."[169] The central and interactive roles of sensory information and affective state are supported by an overwhelming amount of evidence.[63] The affective component of pain incorporates many different emotions. Depression and anxiety have received the greatest amount of attention in chronic pain patients. However, anger and hostility have received considerable interest as a significant emotion in chronic pain patients.[139,170,171] Additionally, the ability to maintain positive affect during times of stress has been investigated in relationship to pain.[172]

In addition to affect being one of the three interconnected components of pain, pain and emotions interact in several ways. Emotional distress may predispose people to experience pain, be a precipitant of symptoms, be a modulating factor amplifying or inhibiting the severity of pain, be a consequence of persistent pain,

or be a perpetuating factor. Moreover, these potential roles are not mutually exclusive, and any number of them may be involved in a particular circumstance interacting with cognitive appraisals. For example, the literature is replete with studies demonstrating that the current mood state modulates reports of pain and tolerance for acute pain.[173] Levels of anxiety have been shown to influence pain severity and complications following surgery and the number of days of hospitalization.[174,175] Individual difference variables, such as AS, have also been shown to play an important predisposing and augmenting role in the experience of pain.[176] Level of depression has been observed to play a significant role in premature termination from pain rehabilitation programs.[177]

Although most of the literature has focused on the relationship between negative affect and pain, research has indicated that the ability to maintain positive affect during stress is an important factor contributing to ongoing adaptation to chronic illness. Positive affect serves to decrease distress in chronic pain patients by broadening the individual's range of affective and cognitive responses permitting a wider range of experiences.[178] Positive affect can serve as psychological immunity in that chronic pain patients may experience more optimal functioning and improved quality of life while living with ongoing pain. Although we will provide an overview of research on the predominant emotions—anxiety, depression, and anger—associated with pain individually, it is important to acknowledge that these emotions are not as distinct when it comes to the experience of pain. They interact and augment each other.

Anxiety

Anxiety and fear-related problems are more prevalent in chronic pain patients than in the general public. The prevalence of any anxiety disorder may be twice as much (35% vs. 18%). Both panic disorder and post-traumatic stress disorder are three times more common in chronic pain patients.[179]

It is common for patients with symptoms of pain to be anxious and worried. This is especially true when the symptoms are unexplained, as is often the case for chronic pain syndromes. For example, in a large study of fibromyalgia patients, between 44% and 51% of patients acknowledged their anxiety.[180] In addition, up to 45% of patients with chronic pain will screen positive for an anxiety disorder.[181] Chronic pain patients with comorbid anxiety may have a lower pain tolerance, be more prone to medication side effects or fearful of having side effects, and be more fearful of pain itself.[182] One study indicated that 40% of patients with Panic Disorder also had chronic pain, particularly head, shoulder, and lower back pain.[183] Panic disorder involves a hyper-focus on somatic sensations that might increase subjective pain sensations. Patients with both chronic pain and panic may engage in more "illness behaviors."[183]

Fear and anxiety are known to have behavioral consequences expressed as escape and avoidance behaviors described previously. Pain-related avoidance and escape behaviors in pain patients may be conceptualized as a set of "safety-seeking behaviors," loosely defined as "behaviors utilized by patients in an attempt to avoid a feared outcome."[184] The revolving model of fear avoidance in chronic pain[128,185] is depicted in Figure 14.1. As the model suggests, pain-related fear and avoidance play a significant role in the interplay between pain, dysfunctional cognitive and affective experience, and disability resulting in the perpetuation of the chronic pain circle. Indeed, pain-related fear avoidance is significantly associated with functional limitation in various life domains and perceived disability in acute and chronic pain patients.[120,186–188]

People with persistent pain may be anxious about the meaning of their symptoms and for their futures—will their pain increase, will their physical capacity diminish, will their symptoms result in progressive disability where they ultimately end in a wheelchair or bedridden? Besides these sources of fear, individuals with persistent pain may be worried that, on the one hand, people will not believe that they are suffering and, on the other, they may be told that they are beyond help and will "just have to learn to live with it." Fear and anxiety will also relate to activities that people with pain anticipate will increase their pain or exacerbate whatever physical factors might be contributing to the pain. As noted in the discussion of the FAM previously, these fears may contribute to avoidance, motivate inactivity, and, ultimately, greater disability.[128] Continual vigilance and monitoring of noxious stimulation and the belief that it signifies disease progression may render even low intensity aversive sensations less bearable. In addition, such fears may contribute to increased muscle tension and physiologic arousal that may exacerbate and maintain pain.

The threat of intense pain captures attention from which it is difficult to disengage. The experience of pain may initiate a set of extremely negative thoughts, as noted previously, and arouse fears—fears of inciting more pain and injury, fear of their future impact. Fear and anticipation of pain are cognitive-perceptual processes that are not driven exclusively by the actual sensory experience of pain and can exert a significant impact on the level of function and pain tolerance.[189,190] Individuals experiencing chronic pain may become hypervigilant to their environment as a way of preventing the occurrence or amplification of pain.

Investigators[26,191] have suggested that fear of pain, driven by the anticipation of pain and not by the sensory experience of pain itself, produces strong negative reinforcement for the persistence of avoidance behavior and the putative functional disability in pain patients. Avoidance behavior is reinforced in the short term through the reduction of suffering associated with noxious stimulation.[192] However, avoidance can be a maladaptive response if it persists and leads to increased fear, limited activity, and other physical and psychological consequences that contribute to disability and persistence of pain.

Studies have demonstrated that fear of movement and fear of (re)injury are better predictors of functional limitations than biomedical parameters or even pain severity and duration.[51,186] For example, Crombez, Vlaeyen, and Heuts[186] showed that pain-related fear was the best predictor of behavioral performance in trunk-extension, flexion, and weightlifting tasks, even after partitioning out the effects of pain intensity. Moreover, Vlaeyen and colleagues[26] found that fear of movement/(re)injury was the best predictor of self-reported disability among chronic back pain patients and that physiologic sensory perception of pain and biomedical findings did not add any predictive value. The importance of fear of activity appears to generalize to daily activities and the clinical experimental context.

Approximately two-thirds of individuals with chronic nonspecific low back pain avoid back straining activities because of fear of (re)injury.[186] For example, fear avoidance beliefs about physical demands of a job are strongly related to disability and work lost during the previous year, even more so than pain severity or other pain variables.[26,193] Interestingly, reduction in pain-related anxiety predicts improvement in functioning, affective distress, pain, and pain-related interference with activity.[82] Fear, pain-related anxiety, and concerns about harm-avoidance all play important roles in chronic pain and need to be assessed and addressed in treatment.

Depression and Depressed Mood

Research suggests that 40% to 50% of chronic pain patients experience depressive symptoms.[194] Conversely, on average, 65% of

depressed individuals also report pain symptoms.[195] Epidemiologic studies provide evidence for a strong association between chronic pain and depression but do not address whether chronic pain causes depression or depression causes chronic pain. Prospective studies of patients with chronic musculoskeletal pain have suggested that chronic pain can cause depression,[196] that depression can cause chronic pain,[197] and that they can be synergistic.[22] A neuroanatomic link between depression and chronic pain via the hypothalamus, amygdala, and anterior cingulate gyrus pathway has been described. Reduced serotonin and norepinephrine are associated with both depression and increased pain sensation.[195]

One fact often raised to support the idea that pain causes depression is that the current depressive episode often began after the onset of the pain problem. The majority of studies appear to support this contention.[198] However, several studies have documented that many patients with chronic pain have often had prior episodes of depression that predated their pain problem by years.[59,60] Some studies also suggest that the pain-depression relationship is not linear but rather is mediated by how patients view their plight. For example, Turk, Okifuji, and Scharff [199] demonstrated that this relationship is mediated by a sense of control and life-interference appraisal of patients. The interaction between cognition and mood in chronic pain makes sense given the presence of individual differences in depression among patients with the same diagnoses at the comparable pain and physical findings.[19]

This is not to say that depression does not exert any contributions to pain. It is well established that depressed people tend to report elevated degrees of pain.[200] Longitudinal studies[60,201] suggest that depression is a risk factor for developing chronic pain. However, these results do not necessarily indicate that depression is the sole cause of pain. Regardless of the causal priority, once a person has a chronic pain diagnosis, it no longer matters which is the cause and which is the consequence—pain or depression. Both need to be treated. This is especially important, considering that depression is not only a significant determinant of pain-related disability.[202] It also drives the costs associated with disability and healthcare utilization upwards.[203]

One important prospective study[60] demonstrated that levels of depression predicted the development of low back pain three years following the initial assessment. Individual who were depressed were 2.3 times more likely to report back pain than those who did not report depression. Depression was a much stronger predictor of incident back pain than any clinical or anatomic risk factors. This has led some investigators to propose that there may exist a common trait of susceptibility to dysphoric physical symptoms (including pain) and negative psychological symptoms (including anxiety and depression). They conclude that "pain and psychological illness should be viewed as having reciprocal psychological and behavioral effects involving both processes of illness expression and adaptation."[60,204] For example, those who experience depression and chronic pain report more intense pain, less control of their lives, more unhealthy coping strategies, and reduced analgesic response to opiate medications.[195] In addition, negative thinking is a common feature of depression and chronic pain.

Research investigating how negative cognition is associated with depression in chronic pain typically shows that depressed pain patients exhibit greater negative thought processes than pain patients without depression.[205,206] Depressed pain patients seem to show greater negativity in thoughts and reduced positive thought processes than nondepressed pain patients.[207] Negative thought process appears to have reciprocal influences such that mood affects pain and conversely pain affects mood. Given the potential contributory role of negative attributions of pain and other somatic symptoms in pain patients, assessment of depression-related negative thoughts in depressed and nondepressed patients experiencing persistent pain seems essential, particularly if these thinking patterns impact how a person responds to pain treatment interventions by concluding "Nothing works for me."[195]

Given the scenario of chronic pain just described, it is hardly surprising that chronic pain patients are depressed. However, it is interesting to ponder the flip side of the coin—why are not *all* chronic pain patients depressed? Turk and colleagues[22,199] examined this question and determined that two factors appear to mediate the pain-depression relationship: patients' appraisals of the effects of the pain on their lives and appraisals of their ability to exert any control over their pain and lives. Those patients who believed that they could continue to function and that they could maintain some control despite their pain were less likely to become depressed. Here we see the interdependence of cognition and affect.

Substance Use

It is uncommon for people with chronic pain to be prescribed analgesics for their pain. When chronic pain does not respond to other therapies, opioid analgesics are often recommended. In recent years, rates of opioid prescriptions have escalated, as have rates of opioid overdose deaths in the United States.[208, 209] Although opioids can provide pain relief, there are concerns about their use in the long-term management of chronic pain, as they carry with them an increased risk for misuse (not in accordance with prescribed directions), abuse (intentional use for a nonmedical purpose), and addiction (use is harmful or has a high potential for harm).[210]

Some individuals with chronic pain use alcohol and prescribed medications to cope with pain and pain-related emotional distress. The DSM-V describes *Substance Use Disorder* (SUD) as a pattern of symptoms resulting from the use of a substance that the individual continues to take despite experiencing problems as a result, with additional specificity around types of substances (i.e. alcohol use disorder [AUD], opioid use disorder [OUD]).[13] The diagnostic criteria include problematic patterns of use leading to clinically significant impairment or distress (e.g. using the substance in larger amounts or over a longer period than was intended, unsuccessful efforts to cut down, strong desire, craving, or urge to use, continued use despite social or occupational consequences, tolerance, and withdrawal).[13] Among people with chronic pain who have been prescribed opioids, rates of misuse average between 21% and 29%; rates of addiction average between 8% and 12%.[208] Studies have suggested that up to 48% of chronic pain patients meet the DSM-V criteria for a SUD.[211,212]

In addition to misuse of prescription medication, alcohol use and misuse are also common among patients evaluated in chronic pain treatment settings, with up to 25% of patients noting a history of current or past alcohol dependence.[209,213] Recently, studies have begun to explore the co-use of alcohol and opioids, as concurrent use has been identified as a contributing factor in many opioid overdose deaths.[214] Studies have noted that 24% to 38% of people with chronic pain who have an OUD have a comorbid diagnosis of AUD.[209] The co-use of alcohol and opioids increases the risk of morbidity and mortality; emergency department visits for opioid-related visits have more serious outcomes with alcohol involvement,[215] and comorbid OUD and AUD has been shown to significantly increase the risk of fatal overdose and liver-related death.[216]

People with a history of SUD comprise a significant portion of chronic pain patients. However, they are often excluded from chronic pain intervention studies.[211] Treatment is thus limited by the lack of data for how best to treat this population. It has been suggested that a multi-disciplinary approach whereby pain reports, analgesia, and activities of daily living are regularly evaluated along with psychological interventions and supervision (urine drug tests, pill counts) may provide some efficacy.[211]

Anger and Hostility

Anger has been widely observed in people with chronic pain.[217] Between 53% and 98% of patients with chronic pain have independently reported feeling some degree of anger, including "bottled up anger."[218,219] One study showed that 88% acknowledged feelings of anger when these were explicitly sought.[220] Several empirical studies provide support for an association between pain intensity, pain severity, and anger/hostility (including trait anger, outward anger expression, hostile ideation, and inability to forgive others) in both healthy and clinical pain populations.[23,170,221–224]

Anger is not necessarily unreasonable—it can be a logical emotional response to the injustice that patients perceive. However, multiple studies have shown that perceived injustice is associated with greater pain, more severe depressive symptoms, pain behavior, and greater disability, with one study showing anger mediating the relationship between perceived injustice and pain intensity.[225–227] Therefore emotional regulation and anger reduction interventions have been suggested for patients with chronic pain.[228–230] This approach may be a good strategy, as anger seems to have an adverse impact on pain if it is suppressed. Kerns et al.[221] noted that the internalization of anger was strongly related to pain, perceived interference, and reported frequency of pain behaviors. Inhibition of anger expression has been found to be related to depression, pain severity, and overt pain behaviors, especially for those with severe pain.[221,231] Similarly, another study [232] showed efforts to suppress provoked anger attenuated blood pressure response to pain and was positively related to greater pain report. However, some patients tend to show strong reservations about expressing socially undesirable emotions that could create interpersonal conflict.[220] For these individuals, it seems that the expression of emotion is under conscious control. They are aware of their anger but choose not to express it. In contrast, some chronic pain patients may lack awareness of their angry feelings and have increased difficulties in recognizing and reporting these feelings.[233] It is thus reasonable to expect that the presence of anger may serve as a complicating factor, increasing autonomic arousal and blocking motivation and acceptance of treatments oriented toward rehabilitation and disability management rather than cure, which are often the only treatments available for chronic pain.[173]

The high prevalence of anger observed is perhaps not surprising, given the frustrations related to persistence of symptoms, limited information on etiology, and repeated treatment failures along with anger toward others (employers, insurance companies, the healthcare system, family members), and anger toward themselves, perhaps, for their inability to alleviate their symptoms and to move on with their lives.[219] Fernandez and Turk proposed that the specificity of targets toward which patients experience angry feelings may be important in the understanding of the relationship between pain and anger.[219] When an individual experiencing pain is angry, there are a range of possible targets (e.g. employer, insurance company, healthcare providers). The presence or intensity of anger directed toward different targets may be differentially related to the chronic pain experience. There may be some targets of anger that are more relevant to the chronic pain experience than others. As will be discussed later, Okifuji et al.[23] found that anger directed toward oneself was particularly common among chronic pain patients evaluated at a pain rehabilitation facility.

Anger in chronic pain has been considered by some to be attributable to enduring personality dispositions associated with unconscious conflicts.[234] In contrast, others have suggested that anger may be a reaction to the presence of recalcitrant symptoms that have been unsubstantiated by objective medical findings and unrelieved by medical treatments.[219] There is some evidence supporting the latter hypothesis. For example, a laboratory study demonstrated that the mere anticipation of pain was sufficient to provoke angry behavioral responses in healthy individuals.[235] Using the cross-lagged design with a clinical sample, Arena et al.[236] found that an increase in pain tends to precede anger, directly contradicting the anger-somatization association.

Frustrations related to persistence of symptoms, unknown etiology, and repeated treatment failures, along with anger toward employers, insurers, the healthcare system, family, and themselves, all contribute to the general dysphoric mood of patients with chronic pain.[23] Okifuji et al.[23] reported that 60% of patients expressed anger toward healthcare providers, 39% toward significant others, 30% toward insurance companies, 26% toward employers, and 20% toward attorneys. The target of anger most commonly acknowledged was anger toward themselves (endorsed by approximately 70% of the sample).

The precise mechanisms by which anger and frustration exacerbate pain are not known. One reasonable possibility is that anger magnifies pain by increasing physiologic arousal.[170] For example, Burns et al.[170] reported the results of a study that demonstrated anger-induced stress produced increased muscle tension, which in turn predicted a greater level of pain severity in chronic back pain patients. It was found that this effect was specific to anger. A measure of depression that was significantly correlated with pain was not associated with increased muscle reactivity.

It is important to know the significant role of negative mood in chronic pain because it is likely to influence treatment motivation and adherence to treatment recommendations. For example, individuals experiencing pain who are anxious may fear engaging in what they perceive as demanding activities; patients who are depressed and who feel helpless may have little initiative or motivation to comply, and patients who are angry with the healthcare system are not likely to be motivated to respond to recommendations from yet another healthcare professional. Thus clinicians who are treating people with persistent pain must focus on their mood states, physical pathology, and somatic factors. Pain cannot be treated successfully without attending to the patient's emotional state. This is true for acute pain, such as pain associated with surgery and persistent pain states.

Conclusion

For the person experiencing chronic pain, there is a continuing quest for relief that often remains elusive, leading to feelings of helplessness, hopelessness, and suffering. Emotional distress may be attributed to various factors, including inadequate or maladaptive coping resources, iatrogenic complications, overuse of medication, disability, financial difficulties, litigation, disruption of usual activities, lack of social support, and sleep disturbance. Thus chronic pain is a demoralizing situation that confronts the person not only with the stress created by pain but with a cascade of ongoing stressors that compromise all

aspects of the life of the person experiencing chronic pain. Living with chronic pain requires considerable emotional resilience and tends to deplete emotional reserve and taxes not only the individual experiencing chronic pain but also the capacity of significant others to provide support. There is a large body of evidence to demonstrate that psychosocial and contextual factors can interfere with or hinder a person's ability to cope with the pain experience.

It is abundantly clear that pain is not a monolithic entity. No isomorphic relationship exists among tissue damage, nociception, and pain report. The variability of patients' responses to nociceptive stimuli and treatment is somewhat more understandable when we consider that pain is a personal experience influenced by attention, the meaning of the situation, prior learning history, and physical pathology. Usually, biomedical factors appear to instigate the initial report of pain. However, over time secondary problems associated with deconditioning may exacerbate and serve to maintain the problem. Inactivity leads to an increased focus on and preoccupation with the body and pain, and these cognitive-attentional changes increase the likelihood of misinterpreting symptoms, the overemphasis on symptoms, and the patient's self-perception as disabled. Reduction of activity, anger, fear of re-injury, pain, loss of compensation, and an environment that perhaps unwittingly supports the pain patient role can impede alleviation of pain, successful rehabilitation, reduction of disability, and improvement in adjustment.

Pain that persists overtime should not be viewed as either solely physical or solely psychological. Instead, the experience of pain is a complex amalgam maintained by an interdependent set of biomedical, psychosocial, and behavioral factors, whose relationships are not static but evolve and change over time. The various interacting factors that affect a person with chronic pain suggest that the phenomenon is quite complex and requires a biopsychosocial perspective.

From the biopsychosocial perspective, each factor outlined throughout this chapter contributes to the experience of pain and the response to treatment. The interaction among the factors is what produces the subjective experience of pain. There is a synergistic relationship whereby psychological and socioenvironmental factors can modulate nociceptive stimulation and the response to treatment. In turn, nociceptive stimulation can influence patients' appraisals of their situation and the treatment, mood states, and how they interact with significant others, including medical practitioners. An integrative, biopsychosocial model of chronic pain needs to incorporate the mutual interrelationships among physical, psychological, and social factors and the changes that occur among these relationships over time. A model and treatment approach that focuses on only one of these three core sets of factors will inevitably be incomplete.

Key Points

- The associations between physical pathology and reports of pain are not highly correlated.
- Reports of pain are not caused by biomedical factors or psychological factors; they are influenced by both.
- Presence of chronic pain impacts all domains of people's lives.
- Although physical pathology may be the cause for initial reports of pain, over time psychosocial and contextual factors play an increasingly important role.
- A range of psychosocial variables (beliefs, appraisals, and expectations) along with affective factors (e.g. anxiety, depression, anger) and contextual factors (e.g. environment, significant others) are related to the experience and reports of pain, adaptation, and disability associated with persistent pain.
- How individuals express their pain and related distress and suffering have a communicative function that can influence the responses of observes and in turn, the responses of others can affect the individual experiencing pain's response.
- Emotional distress may be attributed to various factors, including inadequate or maladaptive coping resources, iatrogenic complications, overuse of medication, disruption of usual activities, lack of social support, sleep disturbance, disability, financial difficulties, and litigation.
- Psychosocial factors can interfere with or hinder a person's ability to cope with the pain experience.
- Attempting to identify the physical basis for reported pain will, although necessary, will be insufficient in understanding and treating patients with chronic pain.
- Responses of significant others can have adaptive or maladaptive influences on the responses of patients.
- An integrative, biopsychosocial model of chronic pain needs to incorporate the mutual interrelationships among physical, psychological, and social factors and the changes that occur among these relationships as they evolve over time.

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15

Comprehensive Approach to Evaluating Patients With Chronic Pain

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Introduction

In the United States, chronic pain is one of the most common reasons adults seek medical care. It has been linked to anxiety, depression, poor mobility, dependence on opioids, and poor perceived health and quality of life. Based on epidemiologic data from the 2016 National Health Interview Survey, the Center for Disease Control and Prevention (CDC) estimated that approximately 20% of adults had chronic pain, and 8% had high impact chronic pain (chronic pain that inhibited daily functioning).[1]

Chronic pain patients are disparate, with varying underlying pathophysiology and widely diverse impacts on quality of life, function, and demands on the healthcare provider and society. All chronic pain reflects an amalgam of biologic, psychological, and social factors that is best assessed with a multidimensional perspective to determine further evaluation and treatment options. This evaluation requires a systematic examination of biomedical contributors to pain and the influences of psychosocial factors, sleep disturbances, physical capability, and medical comorbidities. The physical and psychological evaluation of chronic pain appropriately assesses a range of pathophysiologic and psychosocial processes that may underlie a patient's presentation. This evaluation can be straightforward in a patient with less complicated circumstances but may require a multi-disciplinary team in more complex situations. The basis for the evaluation is a comprehensive assessment that includes a complete and thorough history, physical examination with particular attention to the musculoskeletal and neurologic examination, and related functional limitations, as well as an assessment of psychosocial and contextual factors, including work and social roles.

In this volume, many specific chronic pain disorders are discussed, including particularly relevant physical examination and diagnostic procedures that are appropriate. In this chapter, we attempt to provide a conceptual approach that may serve to guide the assessment of all chronic pain patients regardless of any underlying pathology or disease. Depending on the specific presenting symptoms, imaging and laboratory testing and the focus of the physical examination will vary. We will focus on low back pain (LBP) as one of the most common chronic pain problems, but the principles apply to most chronic pain conditions.

Pain Definition

The International Association for the Study of Pain has recently updated the original 1979 definition to reflect advances in the understanding of pain and to acknowledge that pain may exist even in the absence of objective physical pathology.[2] The revised definition states that pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," and is expanded upon by the addition of six key notes and the etymology of the word pain for further valuable context:

- Pain is always a personal experience influenced to varying degrees by biologic, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Pathophysiology of Chronic Pain

When pain persists beyond the typical time frame for acute pain to resolve, it has transitioned from acute pain to chronic pain, commonly reflecting different underlying mechanisms for the pain resulting in a sustained process. It may no longer be closely linked to actual or threatened tissue damage, even though an insult to the body may have initiated the pain. Processes contributing to the perception of ongoing pain variably include structural and biomedical causes, psychological factors both pre-existing and those arising coincident with the pain, family and social issues, prior pain experiences and trauma, and cognition. The development of chronic pain often involves both central and peripheral sensitization. However, it is often difficult to determine which of these mechanisms is predominant in a clinical context.

A detailed discussion of pain pathophysiology is beyond the scope of this chapter, and further details can be found elsewhere

in this text (see Chapters 8 and 9). We will touch on a clinically based way of thinking of pain classification and the implications for treatment. Pain is commonly classified as nociceptive, neuropathic, peripheral, or centralized, which reflect presumed mechanisms and influence treatment choices and responses, therefore making the distinction between these three broad concepts clinically meaningful.

Nociceptive pain is closely tied to activation by stimuli in the body that cause damage or threaten tissue damage. At least a component of nociceptive pain is associated with a bodily affront (e.g. trauma, surgery, disease progression) and is also associated with a range of chronic musculoskeletal conditions with mechanical, compressive, inflammatory, ischemic, or infectious insults. Medical disorders associated with ongoing nociceptive signaling include degenerative, inflammatory, and neoplastic diseases. Nociceptive pain is typically localized, provoked by use or stimulation of the painful area, and may respond to physical interventions (i.e. rest, heat, ice, bracing, surgical treatment) or traditional analgesics such as anti-inflammatories or opioids. Nociceptive pain often has characteristics familiar to most individuals—aching or sharp with intensity related to stimulation of the area.

Neuropathic pain is caused by a disease or lesion of the somatosensory nervous system that results in pain, often accompanied by increased sensitivity, sensory loss or alteration, and spontaneous or evoked pain.[3] The terms peripheral sensitization (PS) and central sensitization (CS), described in additional detail below, refer to states of abnormally increased responsiveness of the nociceptive system, which can be experienced in multiple painful conditions, including neuropathic pain. Neuropathic pain can be caused by trauma, compression, metabolic disease, toxins or medications, or autoimmune disorders. Neuropathic pain accompanies many conditions.[4,5] The initial insult can be in the peripheral or central nervous system with various conditions: diabetic neuropathy, surgery or trauma, stroke, or spinal cord injury. Chronic radiculopathy is an example of chronic neuropathic pain where there may be no detectable ongoing pathophysiology. Motor or sensory nerve damage typically leads to loss of function in either motor or sensory function, but in the case of neuropathic pain along with loss of function, there is an alteration in the peripheral and/or nervous system resulting in enhanced pain transmission. Patients often describe burning, tingling, or sensitivity with pain provoked by normal stimuli (allodynia) or increased painful response to a stimulus that normally provokes pain (hyperalgesia). Neuropathic pain rarely responds well to traditional analgesic medications.

Although nociceptive and neuropathic pain are familiar to most clinicians, the concepts of CS and PS may be less so. Changes in the central nervous system (CNS) and or peripheral nervous system (PNS) processing of pain are prominent components of many chronic pain conditions and are observed in the transition of acute pain to chronic pain.[6] Altered pain processing in the spinal cord and brain coupled with a decreased ability of the CNS to diminish response to peripheral stimuli known as impaired pain modulation are the key components of CS. These changes amplify the response to peripheral stimuli, at times leading to allodynia (a typically nonpainful stimulus is perceived as painful) and/or hyperalgesia (a normally painful stimulus that has heightened intensity) in a fashion similar to neuropathic pain but without evidence of specific insult or disease of the somatosensory nervous system.

In the case of PS, an afferent nerve in the periphery that has undergone an insult has increased responsiveness with a reduced threshold to stimulation of receptive fields. These changes may be near the injury site or at the dorsal root ganglia and likely involve multiple mechanisms. This leads to increased pain perception and can be a major factor in hyperalgesia or allodynia.[7]

Altered pain processing was initially recognized in less well understood pain conditions, with fibromyalgia (widespread chronic pain and other associated symptoms) as the prototypical example.[8] However, CS has been identified in many other conditions, including chronic back pain, cervical pain and whiplash, osteoarthritis, pelvic pain, and sickle cell disease.[9–14]

Clinicians should consider CS when there are multiple sites of pain, pain provoked with a low level of stimulus without obvious structural problem or associated nervous system injury, or pain that does not respond to traditional treatments (analgesics, modulating procedures—such as steroids or nonsteroidal anti-inflammatory drugs). An increasing number of chronic pain conditions have had CS identified in a subset of those with the condition. Therefore it is likely that many chronic pain patients have at least a component of CS. Findings to distinguish patients with CS from other chronic pain patients can be found using experimental diagnostic tools not typically used in clinical practice—functional magnetic resonance imagine (MRI), quantitative sensory testing, and conditioned pain modulation.

As there are no clinically relevant, commonly used diagnostic tests to determine CS, the diagnosis depends on clinical suspicion, history, and physical examination. Identifying CS is important as it allows for an appropriate treatment focus and can help avoid iatrogenic problems. For example, patients with CS and/or PS may have worsened outcomes after surgery, including more pain, higher complication rates, increased opioid consumption accompanied by increased costs.[15–17]

Assessing Chronic Pain

There is an understanding that given the range of overlapping etiologic, mediating, and moderating factors associated with a diagnosis of chronic pain and subsequent disability, the assessment appropriately takes a broad look from many perspectives. The key elements of the assessment include:

- history of the pain reports and treatments, along with a review of systems and medical, surgical, and social history to put the current pain in context;
- impacts of the pain of function, mood, sleep, social roles, and interactions with others;
- understanding the patient's perspective on the cause of pain, its impact, and expectations;
- physical examination including musculoskeletal and neurologic examinations plus careful observation of pain related behaviors; and
- diagnostic testing.

These assessments are affected by many factors that variably and uniquely interact and include:

- genetics,
- structural or physical changes and pathology,
- CNS and PNS processing such as sensitization and inhibition,
- prior experiences with pain and the medical system,
- psychological factors ranging from psychopathology to coping style,
- belief systems, and
- environmental influences (work, disability, family, societal, financial).[18]

A comprehensive evaluation examines each factor listed above and weighs its importance in the patient experience. The role of genetics in pain assessment and treatment has not yet been clearly defined. Therefore we will focus on a strategy for assessing the other factors that contribute to chronic pain in this chapter.

What Is the History of the Pain?

The first component of assessing patients reporting pain is centered on classic history taking:

- Onset—when did the pain start?
- Location—where does it hurt (all locations)?
- Duration—how long have they had pain; how long does it last when they experience pain?
- Character/description—what does the pain feel like?
- Intensity—how severe is the pain?
- Alleviating factors—what makes the pain better?
- Aggravating factors—what makes the pain worse?
- Radiation—does the pain spread?
- Temporal pattern—does the pain vary throughout the day, has it evolved over time?
- Associated symptoms—how does the pain impact the patient (function, mood, sleep, work, relationships)?

It is important to explore when the patient believes the pain began, whether its onset was insidious vs. attributable to a particular event, trauma, or underlying medical condition, and what the patient believes is the cause(s) of their ongoing pain. Patients' interpretation of their pain provocation and relief is very important to understand the illness narrative whether or not the provider feels it is "logical" or not. Investigating a patients' interpretation of cause, severity, variability over time, exacerbating and relieving factors, and any effects of prior treatment help frame the current situation and future treatment options.

A patient's illness narrative may not align with a providers' biologic model of pain but is critical to understanding the entirety of the patient's experience, which is needed to understand and treat the patient effectively. It is worth noting that in evaluating a patient with chronic pain, the healthcare provider should pay careful attention to certain historical items that are considered only cursorily in other clinical settings. In particular, the healthcare provider should be careful to assess the patient's history for early childhood physical and emotional trauma, early onset of painful conditions, chemical dependency, sleep disturbance and potential for obstructive sleep apnea, apparent severity of incapacitation, and his or her status with respect to litigation and compensation.

Using a body map/pain drawing where patients indicate the location(s) of their pain may be useful. Patients are asked to shade in on the drawing everywhere they experience pain, not just the present reason for evaluation. The assessment can be on paper or in a computerized form. The latter allows for the analysis of the data to make it more quantifiable.[19] This visual display of pain allows for quick recognition of patterns: diffusely filled in diagrams consistent with fibromyalgia, shaded areas that extend from the neck or back to the hand or foot typical of radicular pain, localized and unilateral drawing consistent with sacroiliac joint pain. More widespread pain filled in on a body diagram is associated with both increased disability and poor outcomes after a surgical intervention such as total knee arthroplasty.[19,20]

Assessment of Physical and Medical Factors

A thorough physical evaluation is a basic element in the evaluation of a patient with chronic pain, and while it serves many functions, examination findings are always placed in context with a thorough history. The examination serves many purposes, including:

- assessing function (e.g. gait, strength, range of motion, balance, speed, fluidity) and the patient's awareness of their functional status,
- making diagnoses and collaborating findings with history, imaging, and other diagnostic testing,
- determining if the pain problem is localized (one body region or system) or more generalized,
- determining treatment options and goals (palliation, correction of pathology, functional restoration), and
- determining if referral to a specialist is warranted.

Patients may focus on only their most recent or current pain, or a provider may only investigate the "chief complaint" and not put the pain in the appropriate context if a patient has more diffuse pain. Given the widespread nature of many chronic pain patients' conditions and the possibility of multiple pain sites or recurrent pain, all patients should have a thorough physical examination at their initial visit with an emphasis on musculoskeletal and neurologic examinations well as on their primary area where symptoms are reported. If pain is indeed focal, examining the normal areas confirms that the pain is localized, and the examination can be quickly and efficiently accomplished. Also, evaluating a pain patient depends on the chronicity of the patient's symptoms and the evaluations and diagnostic testing that the patient has already undergone.

To be reasonably specific, the discussion here focuses on evaluating a patient with a chief symptom of back pain. LBP is the most common chronic pain condition with a point prevalence of 13% in the United States and is a leading reason for seeking health care and cause of disability worldwide.[21] LBP is the most common reason for long term opioid use in the United States.[22] Patients with chronic LBP tend to be socioeconomically disadvantaged, visit healthcare providers frequently, and have a high burden of comorbidities.[23] The differential diagnosis of chronic LBP ranges from "non-specific" to serious, potentially life-altering illness. Many structures in the back can cause pain, including muscles, facet and sacroiliac joints, nerve roots, disc, ligaments, or adjacent structures. Thus the differential diagnosis list is long. Psychological and social factors have long been recognized as important and must be appropriately assessed and addressed.[24,25] We will discuss how the differential diagnoses can be further narrowed and a management plan developed through each assessment element.

Physical Examination

The details of physical examination are covered separately in Chapter 18 on specific disorders in this volume; however, we want to re-emphasize the importance of conducting a thorough physical examination of all patients. Decisions about imaging and diagnostic studies should be made when correlation and confirmation is needed between a physical finding, history, and possible pathology.

Red Flag Symptoms Associated With Back Pain

In any initial evaluation of a patient reporting persistent pain, the first concern is always to evaluate for any "red flag" symptoms indicative of a serious underlying medical condition that warrant additional evaluation and possible treatment. Examples of a serious medical condition would include malignancy, infection, significant trauma with damage to spinal elements, or neurologic injury. Symptoms, history, or findings that might represent a red flag include weight loss, profound fatigue, progressive motor or sensory deficits, constant new onset of severe pain, change in bowel

or bladder control, fever, history of cancer or infection, advanced age, prolonged use of steroids, or immune compromised. The presence of multiple red flag symptoms increases the probability of serious underlying pathology.[26,27]

Neurologic Injury

Healthcare providers should be alert for clinical evidence of either radiculopathy, neuropathy, or myelopathy and should recall that a peripheral nerve injury can at times mimic a spinal problem. Radiculopathy is a condition that affects the function of a nerve root, often accompanied by pain and changes in sensation, strength, and reflexes in a specific dermatomal distribution. Myelopathy refers to a neurologic deficit from injury or disease of the spinal cord. On pain history, patients often report a burning or intermittent stinging pain that radiates to various locations throughout their bodies. Patients may identify an inciting event in the lumbosacral region when radiculopathy is because of a disc herniation. Patients may report pain or numbness specifically in a known dermatomal distribution, but at times the complaint is vague, such as "my whole leg is numb," which requires investigation to determine if the complaint represents myelopathy or a more benign vague non-specific sensory change.[28] At other times, patients may complain of numb feet, but on further investigation, it becomes apparent that they have a separate peripheral neuropathy. Similarly, patients may report weakness or loss of fatigue that may represent myelopathy, radiculopathy, another medical condition, or simply deconditioning. Clinicians need to obtain the history in a manner that helps distinguish patterns and narrow the differential diagnosis. Additionally, if a patient has a history of significant trauma associated with the onset of pain or malignancy, urgent attention should be paid to evaluating instability of the spine, compression of neural elements, or metastasis.

Since it is not uncommon for patients to have complex multifactorial pain presentations, it is important to perform a careful sensory, strength, and reflex examination to determine differential diagnosis, need for further diagnostic testing, and treatment options. If needed, electrodiagnostic studies provide more objective evidence for radiculopathy and help distinguish it from peripheral nerve injury. MRI scan may also help provide evidence of an anatomic abnormality of nerve roots or anywhere along the spinal cord.[29] It is important to remember that there are high rates of incidental findings in asymptomatic patients, so imaging should be used to confirm clinical examination findings that are consistent with positive physical pathology. If the patient is asymptomatic for a given finding on examination but has incidental findings on imaging, they are unlikely to be meaningful.[29–31]

Spinal Stenosis

Lumbar spinal stenosis is a common condition (11%-39% of the population) with variable clinical presentation, multiple treatment options, and increased prevalence with age. Lumbar spinal stenosis refers to narrowing of one of three anatomic areas, most commonly of the central canal, but also the lateral recess or neural foramen.[32] The narrowing can be congenital, but more commonly, changes in the structure (disc protrusion, disc height loss, facet arthropathy, osteophytes, ligamentum flavum hypertrophy, spondylolisthesis, fibrosis) result in narrowing that compromises the neural elements. Typically, pain in the back or legs (neurogenic claudication) is brought on by activity such as walking or prolonged standing and relieved with rest or forward flexion. The physical examination findings for lumbar spinal stenosis are often non-specific.

Musculoskeletal Sources of Pain

The differential diagnosis of LBP is complex. Aside from neurologic injury or compression and spinal stenosis, many musculoskeletal structures in the back can be a source of pain: facet joints (paired joints at each level), sacroiliac joints (at the junction of the sacrum and pelvis), ligaments (multiple areas), muscles (back and gluteal), bone (compression fracture), and intervertebral disc (with degeneration). LBP that stays confined to the low back and does not radiate beyond the knee is also known as axial LBP. Commonly musculoskeletal pain can be because of an acute insult, degenerative processes, or chronic deconditioning and poor posture. During history gathering, patients may endorse insidious onset and difficulty with their overall range of motion. On physical examination, pain may be provoked with specific movements or palpation that may help focus the differential diagnosis. It is important to recall that multiple sources of pain can co-exist. In our clinical experience, muscle pain commonly co-occurs with all of the other sources of LBP.

Risk Factors for Poorer Outcome Or Delayed Recovery

Some patients do not respond as well to treatments as the "typical" patient, with persistent pain, dysfunction, and suffering despite treatment that appears to be "appropriate". It is difficult for a clinician to predict who is at risk for minimal benefit from treatment or who will experience slower recovery; the literature does not provide a clear guide. This list of possible risk factors for ongoing, poorly controlled pain includes medical and psychosocial factors. The more of these risk factors a patient has, the more likely they are to have pain that is difficult to treat.

- Identifiable progressive medical condition with known impact on the musculoskeletal or nervous system (e.g. rheumatologic diseases, multiple sclerosis, poorly controlled diabetes)
- More severe structural burden (e.g. failed fusion, uncorrected scoliosis, poly-trauma)
- High pain intensity, particularly pain that does not vary in intensity
- Repeated surgical or other procedures intended to relieve the same pain condition
- Widespread pain, other symptoms, or signs of CS
- Long term opioid use
- Substance abuse (opioid, alcohol, stimulants, tobacco, sedatives)
- Severely compromised function
- Preexisting mental health issues including post-traumatic stress disorder, poorly controlled anxiety, and depression
- Sleep disturbances both sleep apnea and difficulty initiating or maintaining sleep
- Social factors: unstable housing, poverty, low literacy, limited access to medical care, lack of support, physically demanding work conditions
- Medical illness that compromises function or limits treatment option[33,34]

Specific Evaluation for Procedures

The healthcare provider should screen patients for risk of poor response to treatment as outlined above by collecting data in the areas listed above and identify areas requiring additional evaluation or treatment. In addition, patients with several risk factors may be appropriate for team-based treatment by specialists to address what is potentially more difficult to treat pain. Broadly speaking, the information will come from the patient's history, the physical examination, assessment tools, and diagnostic studies.

Diagnostic Studies

Diagnostic studies can shed light on anatomy and structure (imaging including plain x-rays, computed tomography [CT], and MRI scans), nerve and muscle function (electrodiagnostic studies), bone metabolism/structure (bone scans), or systemic illness and inflammation (laboratory testing). For most chronic pain conditions, diagnostic imaging is the most ordered and clinically relevant, but also most overused, with up to two-thirds of studies not clearly indicated. Conversely, patients with "red flag symptoms" may not receive enough/appropriate imaging.[31] Additionally, imaging studies may reveal "abnormalities" including herniated discs and degenerative changes in asymptomatic people,[32] and imaging abnormalities that lack clinical correlation may lead to excessive treatment. While not an exhaustive guide to when/how/what imaging study to order, the following are reasonable and should be considered:

- In significant trauma with ongoing pain but no signs of radiculopathy or myelopathy, plain x-rays evaluate for fracture or instability; addition of MRI if signs or symptoms of neurologic injury.
- Patients with positive red flag symptoms coupled with clinical suspicion should receive MRI if they have any signs of myelopathy or radiculopathy, or severe pain.
- Patients with persistent pain who have not responded to initial conservative treatment are appropriate for screening x-rays and MRI if there are signs of radiculopathy or myelopathy.

CT scans and bone scans have more limited utility, such as identifying an occult fracture or assessing prior fusion hardware

Besides the traditional diagnostic tests discussed above, for patients with ongoing spinal pain who are deemed possible candidates for invasive treatment such as surgical decompression or radiofrequency ablation of the nerves to facet joints or sacroiliac joints, diagnostic local anesthetic blocks to identify a painful structure may have a role. If a patient has significant pain reduction (typically 80%) with image-guided, low volume injection of local anesthetic, it may be assumed that the targeted structure is a "pain generator." For persistent radiculopathy but uncertain imaging, the response to a selective nerve root injection provides important additional information for surgical decision making.[35] For selected patients with axial LBP thought to be from the facet joints, a positive response to a diagnostic medial branch block may lead to radiofrequency ablation of these nerves with a sustained reduction in pain.[36] Less commonly performed and more controversial is diagnostic provocative discography, which we do not recommend.

Summary

The previous section reviews the evaluation of a chronic pain patient with ongoing LBP. We emphasize a thorough history and physical, screening for serious medical conditions and risk factors for possible poor response to treatment, and selective use of diagnostic testing. Such an evaluation will provide a basis for making treatment decisions, deciding on further workup, and appropriate referral to other specialists or treatment providers. However, although necessary, the medical examination is insufficient to understand and develop an appropriate treatment plan for patients presenting with chronic pain. A range of psychosocial, behavioral factors should also be investigated to complement the medical evaluation.

Assessment of Psychosocial Factors

A comprehensive psychological evaluation of a pain patient should be a fundamental component of a multi-disciplinary evaluation. It addresses the specific psychosocial, behavioral, cognitive, and contextual factors such as current mood (anxiety, depression, anger), interpretation of the symptoms, expectations about the meaning of symptoms, and the responses to the patient's symptoms by significant others (e.g. family members, coworkers), each of which contributes to the subjective experience of pain. This information should augment the development of a comprehensive treatment plan.

Elements of the Psychological Evaluation

Interviews

A psychological interview with chronic pain patients is typically semi-structured. A structured format psychiatric interview can be incorporated as a tool to examine psychopathology.[37] However, a psychological interview with pain patients should go beyond assessing psychopathology since its main purpose is to assess a wide range of psychosocial factors (not just psychopathology) related to a patient's symptoms and disability.

Patients' Beliefs and Expectations

It is important to assess patients' expectations regarding diagnosis and management of their pain. Healthcare providers' expectations and patients' expectations may not be aligned, leading to conflict and dissatisfaction with care.

Chronic pain patients' beliefs about the cause of symptoms, their trajectory, and beneficial treatments will have important influences on emotional adjustment and adherence to therapeutic interventions. A habitual pattern of maladaptive thoughts may contribute to a sense of hopelessness, dysphoria, and unwillingness to engage in prescribed activities. The interviewer should also determine both the patient's and the significant others' expectancies and goals for treatment. An expectation that pain will be eliminated completely may be unrealistic and must be addressed to prevent discouragement when this outcome does not occur. Setting appropriate and realistic goals is an important process in pain rehabilitation as it requires the patient to understand chronic pain better and goes beyond the dualistic, traditional medical model—somatogenic vs. psychogenic.

To help patients with chronic pain understand the psychosocial aspects of pain, attention should focus on the patients' reports of specific thoughts, behaviors, emotions, and physiologic responses that precede, accompany, and follow pain episodes or exacerbation, as well as the environmental conditions and consequences associated with their responses in these situations. During the interview, the clinician should attend to the temporal association

of these cognitive, affective, and behavioral events; their specificity versus generality across situations; and the frequency of their occurrence to establish salient features of the target situations, including the controlling variables. The interviewer should seek information that will help to develop potential alternate responses, appropriate goals for the patient, and possible reinforcers for these alternatives.

Patients with chronic pain problems frequently consume various medications to alleviate their symptoms. However, recently the number prescribed has been decreasing, and many patients are becoming disillusioned about the benefits and risks of medications. If patients are taking medication for their pain, it is important to discuss a patient's medications during the interview, as many pain medications (particularly opioids) are associated with side effects that may mimic emotional distress and can have deleterious adverse effects. A clinician, for example, should be familiar with side effects that result in fatigue, sleep difficulties, and mood changes to avoid misdiagnosis of depression. A general understanding of commonly used medications for chronic pain is important, as some patients also may use opioid analgesics to manage dysphoric mood that accompanies pain and its impact. During the interview, potential psychological dependence and aberrant drug seeking behaviors on pain-relieving medications should be evaluated. In most states in the United States, a physician can obtain a record of prescriptions of controlled substances. When in doubt, a psychologist may recommend that such a record be obtained and request urine toxicology screening to rule out aberrant opioid-taking behaviors.[38]

When interviewing a patient with chronic pain, the healthcare professional should not only focus on gathering information that the patient provides but also observe patients' pain behaviors and how they convey information (e.g. facial expressions, movement patterns).[39]

Pain Behavior

Pain is a subjective perception, and there is currently no objective way to know about the experience of pain other than by patients' behavior. Patients display a range of responses that *communicate* to others that they are experiencing pain, distress, and suffering (verbal behaviors such as statements about pain, moaning, and nonverbal behaviors such as limping, grimacing, and rubbing painful body parts). Some of these pain behaviors may be consciously controllable by the patient, whereas others are not. These behaviors may be associated by patients' feelings that their pain is not appreciated as important by significant others, including providers, or they may be the result of physical alterations (e.g. limping associated with structural perturbations). There may be an increase in behaviors when patients feel that others "do not believe them."

Informally, a healthcare provider can observe patients' behaviors during their interviews and examinations. It is useful to observe patients in multiple contexts when possible (e.g. waiting room, ambulating to an exam room, during the interview with the clinician, during physical examination). When patients know they are being observed and are presenting information to a healthcare provider, they may use behavior to convey information in ways most likely to support the impact of their symptoms. They may feel a need to convince the healthcare provider of the severity of their symptoms, functional limitations, and distress. Thus observation of the patient in the waiting room, when ambulating to the examination room, and when departing may allow the clinician to establish the stability and consistency of pain behaviors. When possible, it is useful to observe patients in the presence of a significant other to note differences in behaviors when the significant other is present and absent and how the significant other responds to the patient's pain behaviors. Of course, the clinical interaction is different from the patient's normal environment, so the patient's presentation needs to be considered when interpreting patient behaviors.

Uses of the healthcare system and analgesic medication are other ways to assess pain behaviors. Patients can record the times when they take medication over a specified interval, such as a week. Despite the cautions regarding the use of patient diaries (described below), diaries can provide information about the frequency and quantity of medication and permit the identification of the antecedent and consequent events of medication use. Antecedent events might include stress, boredom, or activity. Examination of antecedents is useful in identifying patterns of medication use that may be associated with factors other than pain per se. Similarly, patterns of response to the use of analgesic may be identified. Does the patient receive attention and sympathy whenever he or she is observed by significant others taking medication? Do significant others positively reinforce taking analgesic medication and unwittingly increase medication use?

Brief Psychosocial Screening

A busy clinician may not have adequate time to completely assess the myriad of psychosocial and behavioral factors demonstrated to be important in chronic pain patients. Thus a brief screening might provide initial information on a range of factors and guide more in-depth evaluation by the provider or guide them in deciding upon referral for a more comprehensive evaluation. The PEG[39] is a brief measure consisting of three questions selected from the Brief Pain Inventory.[40,41] The items ask about pain, emotional distress, and general activity.

Another brief screening interview has been developed—ACT-UP (Activity, Coping, Think, Upset, People's responses).[42,43] Table 15.1 contains a brief set of salient issues covered with the acronym. Generally, a referral for evaluation may be indicated where disability greatly exceeds what would be expected based on physical findings alone, when patients make excessive demands on the healthcare system, when the patient persists in seeking medical tests and treatments when these are not indicated, when patients display significant emotional distress (e.g. depression or anxiety), or when the patient displays evidence of addictive behaviors or continual nonadherence to the prescribed regimen.

TABLE 15.1 Brief Psychosocial Screening: ACT-UP

Activities: How is your pain affecting your life (i.e. sleep, appetite, physical activities, relationships)?
Coping: How do you deal/cope with your pain (what makes it better/worse)?
Think: Do you think your pain will ever get better?
Upset: Have you been feeling worried (anxious)/depressed (down, blue)?
People: How do people respond when you have pain?

Self-Report Inventories

In addition to interviews, several standardized assessment instruments designed to evaluate patients' attitudes, beliefs, and expectancies about themselves, their symptoms, and the healthcare system have been published.[43]

Standardized instruments have some advantages over semi-structured and unstructured interviews. For example, they are easy to administer, require less time, assess a wide range of behaviors, obtain information about behaviors that may be private (sexual relations) or unobservable (thoughts, emotional arousal), and, most importantly, they have been submitted to analyses that permit demonstration of their psychometric properties (e.g. reliability and validity). These instruments should not be viewed as alternatives to interviews. Instead, they are compliments that may suggest issues to be addressed in more depth during an interview or investigated with other measures.

Assessment of Pain

Pain Intensity

Self-report measures of pain often ask patients to quantify their pain by providing a single, general rating of pain: "Is your usual level of pain 'mild,' 'moderate,' or 'severe?'" or "Rate your typical pain on a scale from zero to ten where zero equals no pain, and ten is the worst pain you can imagine." Several simple methods can be used to evaluate pain intensity—numeric rating scale (NRS), verbal rating scales (VRS), and visual analog scales (VAS) using different variations. For example, the Brief Pain Inventory (BPI) includes four individual questions using NRSs—right now, on average, at worst, and at least.[40,43]

NRS and VRS measures tend to be preferred over VAS measures by patients. Greater difficulty completing VAS measures is associated with increased age and greater opioid intake, and cognitive impairment has been shown to be associated with the inability to complete NRS ratings of pain intensity.[42] Other measures are available to assess pain in children and those who are unable to verbally communicate (e.g. stroke patients, mentally-impaired).[44,45]

There has been some concern that retrospective reports may not be valid, as they may reflect current pain severity that serves as an anchor for recall of pain severity over some interval.[46,47] More valid information may be obtained by asking about the current level of pain, pain over the past week, worst pain of the last week, and lowest severity over the last week (e.g. BPI). This has also led to the use of daily diaries believed to be more accurate as they are based on real-time rather than recall. For example, patients are asked to maintain regular diaries of pain intensity with ratings recorded several times each day (e.g. at meals and bedtime) for several days or weeks. One problem noted with paper-and-pencil diaries is that patients may not follow the instruction to provide ratings at specified intervals. Instead, patients may complete diaries in advance ("fill forward") or shortly before seeing a clinician ("fill backward").[48,49] These two reporting approaches undermine the potential validity of diaries. Electronic devices that can prompt patients for ratings and "timestamp" the actual ratings, thus facilitating real-time data capture, can be used as an alternative to paper-and-pencil diaries.[48–50] Although they may be appropriate for research studies, their usefulness in clinical settings may be limited. However, technological advances, including smartphone applications, make the use of these methods more available for clinical use.

Pain Quality

Pain is known to have different sensory and affective qualities in addition to its intensity, and measures of these components of pain may be used to describe an individual's pain experience more fully. The efficacy of pain treatments may vary for different pain qualities. Therefore pain quality measures may identify efficacious treatments for certain types of pain (i.e. nociceptive and neuropathic) but not for overall pain intensity. Assessment of specific pain qualities at baseline also makes it possible to determine whether certain patterns of pain quality moderate the effects of treatment. The Short-Form McGill Pain Questionnaire (SF-MPQ)[51] assesses 15 sensory and affective pain descriptors, and its sensory and affective subscales have demonstrated responsivity to treatment in several clinical trials.[52] More recently, a revision of the SF-MPQ (SF-MPQ-2) was developed to increase the range of items (rated on a zero to ten scale) and items added to assess characteristics of neuropathic pain that have not been adequately assessed in the SF-MPQ-2.[53]

Pain Modifiers

For the majority of people with chronic pain, pain severity varies. Thus it is useful to inquire about what the patient believes makes his or her pain worse. For example, are there specific activities that worsen their symptoms? Are there certain circumstances that contribute to an exacerbation of pain, such as specific activities, interpersonal conflicts? Does pain vary with time of day (e.g. morning, nighttime)? In the same way, it is important to identify factors that magnify or initiate pain episodes and ask about what factors result in reductions in pain. For example, do medication, rest, heat or cold, distraction, or exercise result in reductions of pain severity or even elimination of symptoms for some period? Pain may be influenced by the context or activities being undertaken. Thus it is important to address what factors modify pain, such as the nature of different activities and presence of significant others.

Assessment of Emotional Distress

Chronic pain is frequently associated with emotional distress, particularly depression, anxiety/fear, anger, and irritability. Emotional distress in people with chronic pain presents a challenge when assessing symptoms such as fatigue, reduced activity level, decreased libido, appetite change, sleep disturbance, weight gain or loss, and memory and concentration deficits. These symptoms are often associated with pain per se and have also been considered symptoms of depressive disorders. Therefore improvements or deterioration in such symptoms can result from changes in either pain or emotional distress.

Assessment of Depressed Mood and Anxiety

Several self-report instruments have been developed to assess emotional distress. The BDI and BDI-2,[54,55] the Hospital Anxiety and Depression Scale (HADS),[56,57] and Patient Health Questionnaire) (PHQ)-(9)[58] have well-established reliability and validity in the assessment of symptoms of depression and emotional distress, and they have been used in numerous clinical trials in psychiatry and an increasing number of studies of patients with chronic pain.[59] The HADS includes seven items assessing anxiety and depression. One advantage of the HADS is that it was developed and standardized with medical patients rather than

psychiatric patients. Shorter measures of anxiety (GAD-7)[60] and depression (PHQ-9)[61] have been reported to provide reliable and valid assessments and might also be considered for research and clinical use. Any of these measures are reasonable choices as brief measures of emotional distress.[62]

Assessment of Fear

Many patients with chronic pain, especially those who attribute their symptoms to trauma, fear engaging in activities they believe may either contribute to further injury or exacerbate their symptoms. Avoidance of activities may, in the short term, lead to symptom reduction. Nevertheless, restricting activities over time is likely to lead to decreased functional capacities because of deconditioning. Also, avoidance of activity has the unfortunate consequence of preventing corrective feedback where patients can learn about their erroneous beliefs. Healthcare providers may inadvertently contribute to the avoidance of activity by providing patients with braces that restrict movements and advising them to avoid activities that hurt (i.e. hurt = harm). They may contribute to the patient's fear that something is seriously wrong with their bodies by continuing to order sophisticated diagnostic tests in search of occult physical pathology) or in the description of non-specific diagnostic test results that are interpreted by the patient as representing serious pathology. Self-report measures of fear of movement that might increase pain or physical damage are available (e.g. Tampa Scale of Kinesiophobia [TSK], Fear Avoidance and Beliefs Questionnaires [FABQ]).[61,62]

Assessment of Substance Use and Abuse

A significant percentage of the population frequently use alcohol and illicit substances. Individuals with chronic pain are no different and may use these substances to self-medicate. Opioid misuse is a particular problem for individuals with chronic pain as they may be prescribed opioids to treat their pain.[63] Estimates of the percentage of chronic pain patients who misuse or abuse opioids and other mood altering drugs are variable, but the numbers are not insignificant. Thus healthcare providers need to evaluate their chronic pain patients prior to prescribing these substances and use this information to inform their decisions regarding treatment. Moreover, when they deem an opioid treatment as appropriate, they need to carefully monitor them. Several self-report inventories and structured interview methods have been developed to accomplish these objectives (e.g. Screener and Opioid Assessment for Patients with Pain-Revised [SOAPP-R],[64] Current Opioid Misuse Measure [COMM],[65] Opioid Use Inventory).[66] However, they need to be used with caution as they each have significant limitations.[67]

Assessment of Beliefs, Coping, and Psychosocial Adaptation To Pain

Several measures have been developed to assess pain patients' beliefs, coping, and adaptation. Two particularly potent beliefs (i.e. self-efficacy and catastrophizing) held by patients have been demonstrated to play important roles in chronic pain. *Self-efficacy* (SE) is the conviction that one can perform a certain task or produce a desirable outcome.[68] A major determinant of SE is prior mastery experience. In chronic pain patients, SE positively affects physical and psychological functioning,[69,70] and improvements in SE after self-management and cognitive-behavioral interventions are associated with improvements in pain, functional status, and psychological adjustment. Self-report instruments to assess SE with chronic pain patients have been developed and used in clinical research and practice.[71,72]

Pain catastrophizing can be defined as an exaggerated negative orientation toward actual or anticipated pain experiences. Current conceptualizations most often describe it in terms of appraisal or as a set of maladaptive beliefs.[73] A cognitive and emotional process that involves magnification of pain related stimuli, feelings of helplessness, and a negative orientation to pain and life circumstances includes obsessive rumination about pain and its meaning and magnification of symptoms. These are associated with increase in pain severity ratings and functional disability. Catastrophizing has been an important predictor of response to both acute and chronic pain. Catastrophizing has been associated with increased perceptions of pain severity in both acute[74] and chronic pain severity[75] and disability among groups with diverse pain diagnosis.[76,77]

Several self-report measures of catastrophizing have been developed and shown to have good psychometric properties (Coping Strategies Questionnaire [CSQ],[77] Pain Catastrophizing Scale (PCS)).[78] These measures have been used in both clinical research and contexts and have shown to have predictive validity for disability and response to various treatments. A brief, two-item measure of catastrophizing has been shown to have a high correlation with the longer form and may be helpful as a screening device.[79]

An important caution regarding the term "catastrophizing." Patients tend to view this term as extremely negative and stigmatizing.[80] Although the construct is important, providers should be careful in using this term or referring to self-report measures as measures of catastrophizing when interacting with patients.

Assessing Functional Impact

Physical functioning and activity can be considered from three complementary perspectives, namely, the patient's perspective on his or her functioning (self-report), observation during performance on structure tasks in a clinical or laboratory setting (e.g. timed walking, gait pattern), and objective assessment of activity in the naturally occurring environment (e.g. using technical instruments and devices such as accelerometry).[81,82] Each of these perspectives will provide different information about performance and are complementary. Objective assessment of physical functioning will depend on the nature of the physical capacity and diagnostic condition being assessed. A detailed discussion about this goes beyond the scope of this chapter (see Ware and Sherbourne[83] for a comprehensive review).

Self-Report Measures of Function

Self-report measures have been developed to assess people's reports of their abilities to engage in a range of functional activities such as the ability to walk upstairs, to sit for specific periods, the ability to lift specific weights, perform activities of daily living, as well as the severity of the pain experienced upon the performance of these activities.[82] There are several well-established, psychometrically supported generic (e.g. Short-Form 36 [SF-36])[83] and pain specific (e.g. Brief Pain Questionnaire Interference Scale;[40] Pain Disability Index [ODI];[84] Multidimensional Pain Inventory [MPI]

Interference Scale),[85] and diagnosis back pain specific (Oswestry LBP Disability Questionnaire;[86] Western Ontario McMaster Assessment of Knee and Hip Osteoarthritis [WOMAC])[87] measures of functional status (for an extensive review see Taylor et al.[82])

The Oswestry LBP Disability Questionnaire is a widely used, 10-item scale that asks patients about disability associated with back pain.[86] It has the advantage of being a disease-specific instrument. In general, disease-specific measures are designed to evaluate the specific effects of a disorder that may not be assessed by a generic measure.[81,82] In addition, responses on disease-specific measures will generally reflect the effects of comorbid conditions on physical functioning, which may confound the interpretation of change over the course of a trial when generic measures are used. Disease-specific measures may be more sensitive to the effects of treatment on function, but generic measures provide information about physical functioning and treatment benefits that can be compared across different conditions and studies.[82,88] Each of these approaches has strengths. Decisions regarding whether to use a disease-specific or a generic measure or some combination will depend on the purpose of the assessment. For individual patients in clinical practice, it would be most appropriate to use measures developed on samples with comparable characteristics. If the healthcare provider wishes to compare across a group of patients, then one of the broader-based pain specific measures should be considered. If the assessment is being performed as part of a research study, some combination might be appropriate to compare chronic pain samples with a larger population of people with diverse medical diseases (e.g. SF-36[83]).

One aspect of physical functioning that is particularly important to those with chronic pain is sleep.[89] Pain is frequently reported to have a significant impact on sleep quality and duration.[90] Patients being evaluated should be asked about their sleep, and depending on the information acquired during an interview, more detailed methods are available to assess sleep objectively using formal sleep laboratory evaluation, accelerometry, and self-report measures (e.g. Medical Outcomes Study [MOS] sleep scale).[91]

Besides physical functioning, work status is important for LBP patients. In the absence of a standard instrument, and when appropriate, clinicians assessing LBP patients should investigate the following issues regarding work: (1) Is the patient working? (2) If the patient is not working, is this related to his or her health? (3) How long has the patient been out of the workforce, and what is their work history? (4) Is he or she receiving any work disability benefits? Which ones? (5) Have they been trained for their work and skills/knowledge required? and (6) What does/did it mean to them (e.g. source of pride, onerous)?

A significant proportion of individuals involved in LBP injuries file personal injury claims. There is some evidence that injured workers with workers' compensation claims respond more poorly to a variety of treatments compared to individuals with these same medical conditions but without workers' compensation claims.[92] Research on the relationship between litigation and clinical course, however, has been contradictory. For example, several studies have reported a negative effect of attorney involvement and litigation on recovery from whiplash disorders.[93,94] Others have not supported the prognostic role of these factors.[95] It is beyond the scope of this chapter to review the often contentious literature on the effect of litigation/attorney involvement on outcomes of chronic pain.[96–100]

Assessment of Physical Capacity

The physical capacities of pain patients are typically assessed by physical and occupational therapists. In some clinical settings, evaluation protocols are developed informally by individual therapists, sometimes in conjunction with a physician. In other settings, formal assessment protocols are used. Although the validity of such protocols has been questioned,[82] they are frequently used, particularly when injured workers are evaluated. Such evaluations obtain objective information about the capabilities of patients. In clinical settings, this information is used in the planning of rehabilitative treatment. In more adversarial settings (e.g. workers' compensation), physical capacities data are used when adjudicative decisions about claims are made.

Assessment of Social Supports

Social support factors are construed as factors in the social (interpersonal) environment that influence people independent of their individual psychological characteristics. The availability, nature, and quality of social supports and the responses of significant others play an important role in how individuals respond to their pain. As noted, patients' pain behaviors communicate to others the severity of their symptoms, emotional distress, and suffering. Since these behaviors are observable, they are capable of eliciting responses. How significant others respond to patients' behaviors may be adaptive (e.g. encouraging) or maladaptive (e.g. punishing, solicitous). Several instruments have been developed to assess patients' perceptions of the responses of others to their plight (e.g. MPI-Spouse Response Scale).[85] For example, there is good evidence that pain patients generally demonstrate more dramatic pain behaviors when they are in the presence of solicitous spouses.[101]

Conclusion

Pain and associated symptoms result from a complex interplay of factors. Assessment and treatment of chronic pain can be complicated by the web of influential factors that modulate the overall pain experience and associated disability. Pain research in the last half-century has repeatedly shown that pain is not just a physiologic phenomenon and that a range of "person variables," such as psychosocial, environmental, and behavioral factors, play a significant role in determining the occurrence, severity, and quality of pain. Given the multifactorial nature of chronic pain, adequate assessment requires a comprehensive approach. This chapter discussed the assessment of medical factors, altered CNS processing, psychological factors, and social factors in patients with chronic pain. We described several self-report inventories that can be used in conjunction with interviews and medical examinations. As we have repeatedly stressed, an adequate assessment of patients with chronic pain means the evaluation of the person with the symptoms and not just the symptoms and physical pathology. Although there is no shortcut in this, the delineation of relevant medical, psychosocial, and behavioral factors contributing to pain in a patient is critical in planning and executing a successful treatment plan. We did describe some brief measures that might be informative regarding areas worthy of further investigation.

Key Points

- Assess the person and not just the reported pain.
- A thorough history and physical, screening for serious medical conditions and risk factors for possible poor response to treatment, and selective use of diagnostic testing are essential ingredients of a comprehensive assessment of patients with chronic pain. Although necessary, they are not sufficient.
- Diagnostic imaging can be overused and is appropriate to confirm information gathered during the history taking and physical examination.
- A range of psychosocial, behavioral, and contextual factors all contribute to the experience of chronic pain and pain related disability. These factors need to be evaluated to better understand patients with chronic pain and contribute to the treatment plan.
- Patients' beliefs about the cause and meaning of their symptoms and expectations for treatment are important to investigate before prescribing any treatment as their erroneous beliefs, and unrealistic expectations can undermine patients' engagement in prescribed treatment regimens and outcomes.
- Observation of patients during clinical interactions can provide useful information about patients' conscious and nonconscious motivations.
- Self-report measures can be used to acquire information about patients' beliefs, mood, and activity.
- Self-report of functional activities may not provide accurate information of physical capabilities, and more objective means of assessment should be considered as complements. However, self-reports of function are important sources of information because they convey the patients' perceptions even if not consistent with objective measures and should not be dismissed.

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16

Mechanism-Based Treatment and Precision Medicine

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Introduction

The advancement of pain medicine is driven by the continual search for new and innovative solutions to a wide range of chronic pain conditions that affect more than 50 million Americans.[1] An important approach is to better understand the mechanisms of pain and factors that determine the transition from acute to chronic pain states. By doing so, new and effective mechanism-guided preventive measures and therapeutics may be discovered, developed, and translated to serve the urgent needs of our patients. However, mechanism-guided therapies often cannot achieve the desired therapeutic outcomes for several reasons. First, our understanding of pain development, maintenance, and chronification or resolution is limited, as the cellular and molecular mechanisms of these pain stages in different pain conditions are not fully understood. Second, most complex pain conditions are determined by an interplay of multiple mechanisms, including other comorbidities, psychological factors, and social determinants. Third, the mechanisms of many therapies are complex, often with multiple targets and mechanisms associated with significant off-target side effects. Fourth, mechanism-guided therapies typically do not consider individual variability in genetics, sex, tolerability to treatment, and many developmental and environmental factors. For these reasons, the future of pain therapeutics will be personalized precision medicine, an emerging approach for disease treatment and prevention that considers individual variability in genetics, prior history, environment, and lifestyle. Thus precision pain medicine has great potential to enhance the biopsychosocial modal of patient-centered care.[2] In the biologic sphere, effective mechanism-based treatment depends on proper assessment and accurate diagnosis/differential diagnosis that is based upon the anatomic location/structure, the pathologic nature, the cellular, molecular mechanisms, and genetic predisposition of pain. Patient phenotyping by quantitative sensory test has been shown to identify subgroups that better respond to specific pharmacologic treatments. At the psychosocial levels, clinical outcomes are highly influenced by such psychological factors as catastrophizing, depression, and anxiety, and social factors such as lifestyle, social economic status, and access to care. Often, these psychosocial factors may be predominant in determining patients' outcomes.

Evidence-based medicine, by definition, is the conscientious, explicit, judicious, and reasonable use of best evidence in decision-making about the care of individual patients.[3] Evidence-based pain therapy integrates clinical experience and patient values with the best available research information. Thus mechanism-guided treatment and precision medicine are the foundation for the development of evidence-based pain therapy and clinical practice guidelines, which consider individual variability and other confounders to inform clinical decision-making between clinicians and patients with the goal to maximize therapeutic benefits and minimize side effects. Given the futuristic perspective of precision pain medicine, it will be discussed in a dedicated part of this chapter (Precision Pain Medicine Section).

A comprehensive review of all mechanism-based therapies in pain medicine is beyond the scope of this chapter. Instead, we will concisely review the commonly used and mechanism-based therapies that include pharmacologic treatments, interventional procedures/surgeries, and physical/cognitive/and behavioral therapies. We will focus on the recent development of promising and innovative new therapies using biologics such as monoclonal antibodies and cell therapies and neuromodulatory approaches such as spinal cord stimulation (SCS). It cannot be overemphasized that all of these treatment modalities have to be guided by proper assessment and accurate diagnosis and tailored to each patient's needs as part of patient-centered, multi-disciplinary, and integrated care.[4]

Current and Developing Mechanism-Based Treatments

State-of-the-art therapies in pain medicine are used to modulate the transduction, conduction, transmission, and perception of pain sensation through specific molecular, cellular, and neural network (circuitry) targets (Table 16.1). At the molecular level, pain therapies may work by affecting ion channels, receptors, and other critical signaling molecules. At the cellular level, pain treatment may influence the firing rate and firing pattern of neurons and the state of inflammatory and immune cells, including glia, microglia, and macrophages. At the circuitry level, therapies may influence the function and connectivity of ascending pain pathways, interneurons in the spinal cord, descending modulatory pathways from the brainstem to the spinal cord, and various regions of the brain responsible for the sensory and emotional aspects of pain perception, and behavioral reaction and adaptation to pain.

Pharmacologic Therapies

Current Treatments

Current pharmacologic therapy involves the use of local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-depressants, anti-convulsants, muscle relaxants, and opioids (Table 16.1), among other drugs. These therapies achieve analgesic effects through a wide range of mechanisms. For example, local anesthetics reversibly block pain impulses by blocking voltage-gated sodium channels. Anti-inflammatory drugs selectively or non-selectively inhibit cyclooxygenases (Cox-1 and Cox-2) to reduce inflammation and sensitization of pain. Most muscle relaxants act centrally. They may activate α2-adrenergic receptor (tizanidine), leading to reduction of excitatory amino acid release from spinal interneurons,[5] or to inhibit 5-HT2 receptor (cyclobenzaprine), leading to diminishing serotonergic descending tone in the spinal cord ventral horn.[6] Anti-convulsants block sodium (e.g. carbamazepine, oxcarbazepine, topiramate, valproic acid) or calcium channels (gabapentinoids, valproic acid).[7,8] Opioids activate μ, delta, or κ opioid receptors to produce analgesia.[9] Anti-depressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g. duloxetine, tramadol, and TCAs), selective serotonin reuptake inhibitors (SSRIs, e.g. Fluoxetine), and selective norepinephrine reuptake inhibitors (NRIs, e.g. tapentadol), activate the descending inhibitory pathways to dampen nociceptive transmission. It is common for one drug to have multiple therapeutic targets or mechanisms. For example, tapentadol acts as a norepinephrine transporter inhibitor and a μ-opioid receptor agonist; Gabapentin primarily works by blocking the α2δ1 subunit of voltage-gated Ca^{2+} channels,[10] but may also modulate other targets such as transient receptor potential channels and N-methyl-D-aspartate (NMDA) receptors.[11] In addition, it may also inhibit γ-aminobutyric acid (GABA) release in the locus coeruleus and stimulate noradrenaline-mediated descending inhibition in the spinal cord.[12]

Monoclonal antibodies are antibodies produced by identical immune cells that are clones of a unique parent cell. Given their high selectivity and long half-lives (weeks), monoclonal antibodies are emerging as the main type of pain therapeutic for multiple targets. Monoclonal antibodies antagonizing the calcitonin gene-related peptide (CGRP) signaling pathway represent a novel and mechanism-specific approach to the prevention and treatment of migraine headaches, as CGRP plays a critical role in neurogenic inflammation and the pathogenesis of migraine.[13] Monoclonal antibodies against CGRP (fremanezumab, galcanezumab, and eptinezumab)[14–16] or CGRP receptor (erenumab)[17,18] have shown efficacy in preventing or aborting migraine headaches in high-profile controlled trials without safety issues to date (Table 16.1).

Treatments Under Development

It is noteworthy that Oliceridine is recently FDA-approved for short-term use to treat moderate to severe pain in hospitals or other controlled clinical settings.[19] (Table 16.2). However, pharmacologic inhibitors for these new targets for G protein-coupled receptors, ion channels, and enzymes have achieved limited success.[19] For example, pre-clinical studies have indicated an important role of p38 mitogen-activated protein kinase (MAP) kinase in microglia activation and the pathogenesis of pain.[20] However, most of the p38 inhibitors have failed in clinical trials for different disease conditions either because of poor pharmacokinetic profiles or lack of selectivity.[21] Nerve growth factor (NGF) plays an important role in inflammatory pain[22–24] and cancer pain,[25] NGF monoclonal antibodies such as Tanezumab, Fulranumab, and Fasinumab are developed for managing chronic pain in humans and in dogs and cats.[26] Anti-NGF treatment alleviated joint pain in patients with osteoarthritis, but also resulted in joint safety events. Further research is needed to determine the clinical importance of these efficacy and adverse event findings.[27] The voltage-gated

TABLE 16.1 Therapeutic Agents in Clinical Practice

Therapeutic Target/ Mechanisms	Representative Drugs
μ opioid receptor agonists	Opioids: Morphine, Hydrocodone, Hydromorphone, Methadone, Fentanyl, Tramadol, Tapentadol
Cyclooxygenase (Cox-1 and Cox-2) non-selective inhibitors	Meloxicam, Ibuprofen, Naproxen
Cox-2 selective inhibitor	Celecoxib (NSAIDs)
Voltage-gated sodium channels: non-selective blockers	Antiepileptic drugs: Carbamazepine, Oxcarbazepine; Local anesthetics: Lidocaine, Bupivacaine, Ropivacaine
Voltage-gated calcium channels: $Ca_v2.2$ blocker	Ziconotide (used intrathecally for cancer and chronic non-cancer pain)
Ca^{2+} channel α2δ1 subunit blocker	Gabapentinoid: gabapentin, pregabalin (Antiepileptic drugs)
NMDA Receptor antagonist	Ketamine, a dissociative anesthetic
5HT1B/D agonist	Triptans for Migraine
5HT/NE transporter, serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine (Anti-depressants); Tramadol, Tricyclic anti-depressants: Amitriptyline, Nortriptyline, Desipramine
5HT transporter, serotonin selective reuptake inhibitors (SSRIs)	Fluoxetine (alleviation of nociceptive pain and attenuation of opioid tolerance and dependence)
Norepinephrine transporter, Norepinephrine reuptake inhibitors (NRI)	Tapentadol
Adrenergic α2 receptor agonist	Tizanidine (muscle relaxant)
5HT2 receptor antagonist	Cyclobenzaprine (muscle relaxant)
Synaptosome-associated protein (SNAP-25)	Botulinum toxin A
Vesicle-associated membrane protein (VAMP)	Botulinum toxin B
CGRP receptor monoclonal antibody	Erenumab for migraine headache prevention
CGRP monoclonal antibodies	Fremanezumab, Galcanezumab, and Eptinezumab for migraine headache treatment and prevention

TABLE 16.2 Therapeutic Targets That Have Been Or Are Being Tested

Therapeutic Target/ Mechanisms	Representative Agents
TRPV1 antagonists (nociceptor & pain transduction)	MK2295, SB705498, GRC6211, AMG517, ABT102, ADZ1386
$Na_V1.7$ sodium channel inhibitors (nociceptor excitability & pain conduction)	PF-05089771, CNV1014802, funapide, DSP-2230, Ralfinamide
$Ca_V3.2$ T-type calcium channel inhibitors (synaptic transmission)	TTA-P2; epipregnanolone [(3β,5β)-3-Hydroxypregnan-20-1]
K_V7 potassium channel activator (nociceptor excitability)	Retigabine, flupirtine
CCR2 chemokine receptor antagonists (neuroinflammation)	RS504393, AZD2423, RAP-103
NMDA receptor blockers (synaptic transmission)	Nitrous oxide, dextromethorphan
p38 MAP kinase inhibitors (intracellular signal transduction, microglial activation, neuroinflammation)	Acumapimod (BCT197), Neflamapimod (VX-745), PH-797804, dilmapimod (SB-681323), losmapimod (GW856553X), Talmapimod
NGF monoclonal antibodies (pain sensitization)	Tanezumab, Fulranumab, Fasinumab
Biased μ-opioid receptor agonist (pain transmission)	TRV130 (Oliceridine)
k-opiod receptor agonists (pain transmission)	Pentazocine; JT09 (agonists, peripheral analgesic effects without central side effects)
P2X purinergic receptors antagonist (pain sensitization)	AF-219 (P2X3 antagonist)
GABA receptors subtype-selective modulator (pain transmission)	NS11394 (subtype-selective positive allosteric modulator at $GABA_A$ receptors)

sodium channel subtype Nav1.7 is one of the best validated targets for human pain.[28] However, the effect of a selective, peripherally restricted Nav1.7 sodium channel blocker PF-05089771 was smaller than that seen with pregabalin.[29]

Nonpharmacologic Therapies

Interventional Procedures

Interventional procedures employ an array of therapeutic mechanisms. Nerve blocks with local anesthetics, often combined with a corticosteroid, reversibly block nociceptive afferents and reduce irritation/inflammation of the target nerve. Since nerve blocks often only provide short-term therapeutic effects, nerve ablations are sometimes used to provide longer term relief of joint pain (e.g. facet joint, sacroiliac joint, knee, hip, shoulder, and intervertebral disc), neuropathic pain (e.g. trigeminal neuralgia, nerve entrapments), or visceral pain (chronic abdominal or pelvic pain) through radiofrequency denervation, cryoneurolysis, chemoneurolysis, or balloon compression. These procedures provide an irreversible block of nociceptive afferents until nerve regeneration and reinnervation occur.

Surgical Approaches

A wide range of surgical procedures are performed to treat pain by decompressing specific nerves that are compressed or entrapped. Examples include microvascular decompression for trigeminal neuralgia, laminectomy or minimal invasive lumbar decompression for spinal canal stenosis, foraminotomy for foraminal stenosis, and discectomy for intervertebral disc encroachment of the spinal nerve root. These surgeries are performed to mitigate physical compression and/or chemical irritation of the target nerve, improve the blood circulation of the nerves, and relieve pain and other symptoms.

Physical/Cognitive/Behavioral Therapies

The role of physical, cognitive, and behavioral therapies is increasingly recognized in pain management. Although the mechanisms for most of these therapies remain to be elucidated, influential hypotheses or theories have been proposed and frequently cited. Physical therapy, such as exercise, manual therapy, and transcutaneous electrical nerve stimulation, can be used to target specific changes in peripheral tissues and nociceptors, neuropathic pain signs and symptoms, reduced central inhibition and enhanced central excitability, psychosocial factors, and alterations of the movement system.[30] These five categories of pain mechanisms (nociceptive, central, neuropathic, psychosocial, and movement system) are often cited in physical therapies. Cognitive behavior therapy (CBT) is based on the belief that thought distortions and maladaptive behaviors play a role in the development and maintenance of psychological disorders and disability, including chronic pain disorders, and that symptoms and associated distress can be reduced by teaching new information-processing skills and coping mechanisms. Clinical trials and clinical practice support the use and efficacy of these treatments in specific patient populations.[31–33]

Neuromodulation

The field of neuromodulation has witnessed the fastest progress in innovation and clinical application.[34] New modalities such as high frequency spinal cord dorsal column stimulation,[35,36] burst stimulation,[37,38] high density stimulation,[39] differential targeted multiplexed stimulation,[40,41] closed-loop stimulation,[42,43] dorsal root ganglion stimulation,[44] peripheral nerve stimulation,[45] vagus nerve stimulation (VNS),[46,47] and transcranial direct current stimulation[48] among others have yielded exciting results. Several randomized comparative trials have recently been conducted to provide strong evidence in support of clinical applications of several new modalities of neuromodulation to treat a wide range of severe and refractory pain conditions. Meanwhile, investigations have also been intensified to better understand the mechanisms of action of these modalities of neuromodulation.

Progress in Neuroimmune Modulation of Pain and Emerging Targets

Over the past decade, we have seen tremendous progress in revealing neuronal mechanisms of pain. First, using transcriptional profiling analysis at the whole population and single-cell levels, studies have

revealed molecular diversity of primary sensory neurons, including nociceptors in mouse dorsal root ganglia (DRG).[49–52] Second, using the cutting-edge technologies of optogenetics and chemogenetics, we have greatly expanded our knowledge of pain circuits, including the circuit that mediates "gate control" and mechanical allodynia in the spinal cord.[53–56] These circuits also modulate central sensitization, an enhancement of pain processing within the CNS (spinal cord and brain). Notably, central sensitization can manifest not only as an increase in excitatory neurotransmission but also as a disinhibition (i.e. reduction or loss of inhibitory synaptic transmission in the central pain circuits).[57] Central sensitization can rapidly open the spinal cord "gate," enabling tactile stimulation to induce mechanical allodynia (tactile allodynia), a cardinal feature of many chronic pain conditions.[56]

Glia Activation, Gliopathy, and Neuroinflammation in Chronic Pain

Our neuro-centric view of pain is changing, as we have seen an exponential increase in publications on neuroimmune modulation of pain.[58–61] Especially, activation of glial cells, such as microglia and astrocytes following painful insults (e.g. nerve injury), is emerging as a key mechanism for the pathogenesis of pain.[59,62–66] In addition to neuropathy, "gliopathy" is being recognized as a driving force for the development and maintenance of chronic pain.[67] Bidirectional signaling between the immune and nervous systems has been revealed in chronic pain condtions.[61,68,69]

Our expanded knowledge in glial modulation of pain has led to increasing appreciation of "neuroinflammation" as a key contributor to central sensitization and chronic pain. Compared to inflammation, neuroinflammation is a local inflammation in the nervous system. Neuroinflammation can be characterized by 1) glia activation in the peripheral nervous system (PNS) (e.g. Schwann cells and satellite glial cells) and the CNS (e.g. microglia and astrocytes), 2) infiltration of immune cells (e.g. macrophages and T cells), and 3) production of inflammatory cytokines and chemokines.[70–72] It is important to define different types of inflammation, as they play different roles in different stages of pain and in different types of pain.[13] For example, neurogenic inflammation is evoked by activation of nociceptive primary afferents and contributes to pain conditions such as headache and complex regional pain syndrome (CRPS). Blood testing could detect inflammation but might be difficult to assess neuroinflammation. Notably, neuroinflammation can still be present in the PNS and CNS, even when inflammation is largely resolved. Thus neuroinflammation plays an important role in pain chronification.[70] Neuroinflammation could be detected in the cerebrospinal fluid (CSF); and circulating CSF can spread pain to remote parts of the body. It is conceivable that neuroinflammation contributes to widespread chronic pain conditions, such as fibromyalgia and temporomandibular disorders.[73]

The most critical step to understanding neuroimmune and neuro-glial interactions in pain modulation is to figure out how inflammatory mediators (IFMs, such as cytokines and chemokines), produced by immune cells and glial cells, regulate neuronal activities in the pain circuit. It was generally believed that cytokines such as IL-1β enhance pain states via induction of cyclooxygenase-2 (COX-2) and subsequent production of prostaglandins (e.g. PGE2), and this process occurs both in the PNS and CNS.[74] However, COX-2 inhibition is not so effective in treating chronic pain such as neuropathic pain. Instead, recent progress has demonstrated a direct modulation of pain transmission by cytokines, as neurons express cytokine receptors (e.g. IL-1 receptor [IL-1R1], IL-6 receptor [IL-6R], and tumor necrosis factor [TNF] receptors p55 [TNF-RI] and p75 [TNF-RII]). Strikingly, cytokines are powerful neuromodulators and synaptic modulators: electrophysiologic evidence shows that IL-1β, IL-6, and TNF can rapidly (within a minute) and potently (at low nM range concentration, as compared to mM range of the neurotransmitter glutamate) modulate both excitatory and inhibitory synaptic transmission.[75,76] This finding has changed our view of the time-scale and effectiveness of glial modulation of pain circuits.

Proinflammatory Cytokines and Chemokines

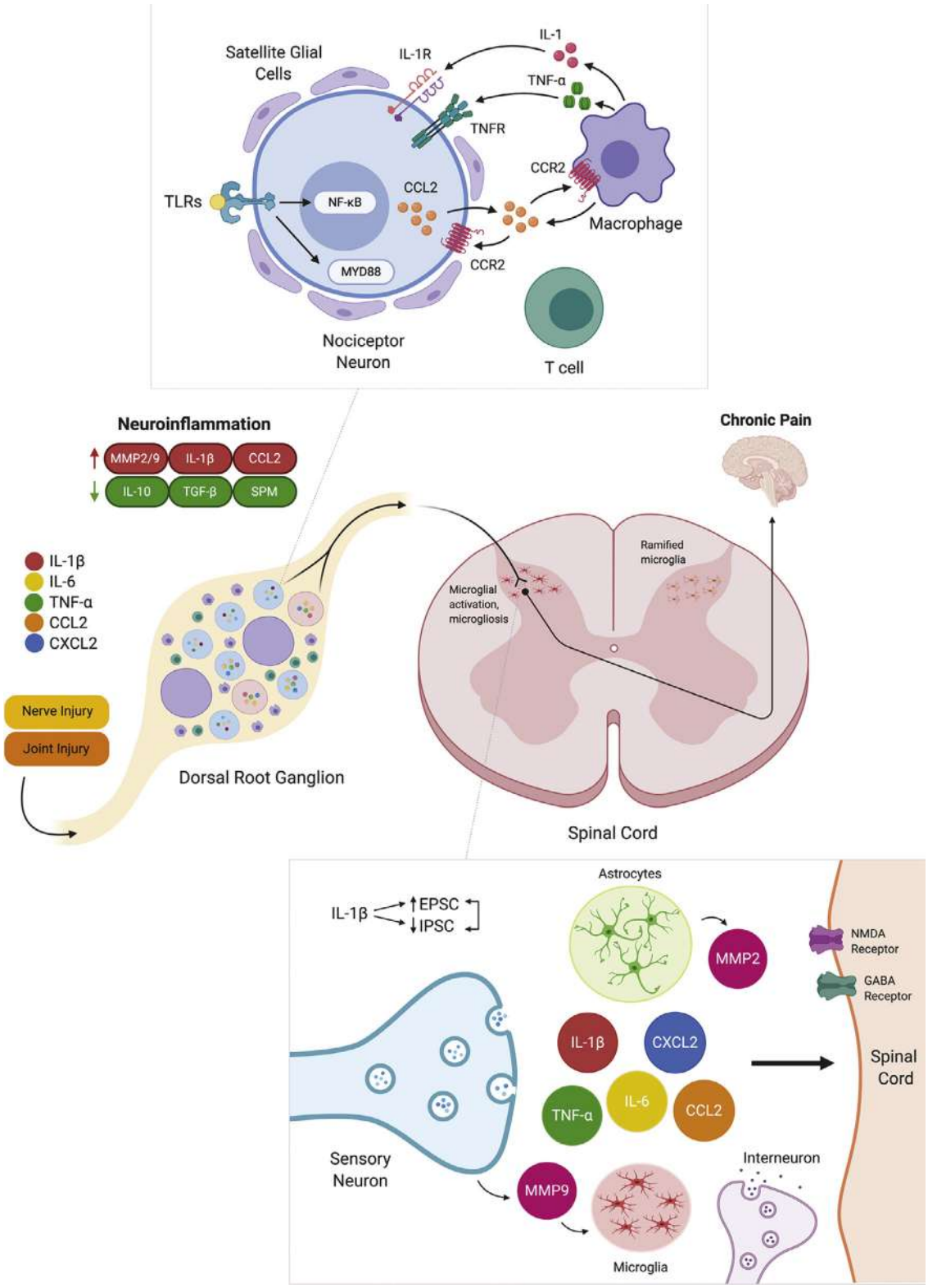
Upon activation, glial cells produce proinflammatory cytokines such as TNF, IL-1β, and IL-6 to promote pain.[63,64,77] IL-1β regulates different types of pain conditions, such as inflammatory pain, neuropathic pain, and cancer pain.[61] Administration of recombinant IL-1β via different routes, such as perineural, intraplantar, and intrathecal administration of IL-1β itself, is sufficient to elicit pain hypersensitivity, while blocking IL-1β signaling via genetic deletion of the IL-1 receptor (IL-1R) or intrathecal injection of IL-1R neutralizing antibodies or antagonists attenuate pain in a variety of rodent models.[61,64] Intriguingly, central (intrathecal) but not peripheral administration of the IL-1 receptor antagonist anakinra at 16 weeks post-bone fracture reduced chronic postoperative pain in rodents,[78] supporting an important role of IL-1β signaling in the maintenance of chronic pain. In contrast to IL-1β upregulation, IL1-receptor antagonist (IL1-Ra), a natural inhibitor of IL-1β secreted by immune cells, epithelial cells, and adipocytes, which opposes the actions of IL-1β, is downregulated in chronic pain conditions.[79]

Chemokines are small cytokines and signal through G protein-coupled receptors (GPCRs). As two of the best studied chemokines, CCL2 and CXCL1 are produced by astrocytes in the spinal cord and primary sensory neurons. CCL2 and CXCL2 promote inflammatory, neuropathic, and cancer pain via their respective CCR2 and CXCR2 receptors that are expressed by neurons.[80–83]

Mechanistically, glia-derived cytokines (TNF, IL-1β, IL-6) and chemokines (CCL2 and CXCL1) can rapidly evoke central sensitization and produce pain by both enhancing excitatory α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA-mediated synaptic transmission and concurrent inhibition of GABAergic and glycinergic neurotransmission in the superficial layers of the dorsal spinal cord.[75] Additionally, these cytokines and chemokines elicit peripheral sensitization by increasing the activities of key ion channels such as transient receptor potential (TRP) channels (TRPA1 and TRPV1) and voltage-gated sodium channels (Nav1.7-1.9)[70,84] (Figure 16.1).

Anti-inflammatory Cytokines

IL-10, produced by various immune cells, has been extensively investigated for its anti-inflammatory and antinociceptive actions. In the early life of rodents, neuropathic pain is masked by IL-10-mediated anti-inflammatory regulation in the spinal cord, which can be unmasked by spinal anti-IL-10 treatment.[85] Sustained production of IL-10 in the spinal cord via gene therapy produces long-term relief of neuropathic pain in rats.[86] Exercise has been shown to alleviate pain through the endogenous release of IL-10.[87] IL-10 is an important mediator for neuron-glial interaction. The anti-inflammatory cytokine TGF-β1 is downregulated



• **Figure 16.1** Schematic illustration of neuroimmune modulation of chronic pain in the peripheral nervous system (PNS; dorsal root ganglion) and central nervous system (CNS; spinal cord). Painful insults, such as nerve injury and joint injury (arthritis), activate glial cells, including satellite glial cells in the dorsal root ganglia and microglia and astrocytes in the spinal cord, and infiltration of immune cells such as macrophages and T cells, leading to neuroinflammation in the PNS and CNS. Neuroinflammation is associated with increased production of proinflammatory cytokines and chemokines (interleukin [IL]-1β, IL-6, tumor necrosis factor [TNF]-α, CCL2, CXCL1) and decreased production of antiinflammatory cytokines (IL-10, transforming growth factor [TGF]-β) and specialized pro-resolving mediators (SPMs, e.g. resolvins and protectins). SPMs may serve as novel biomarkers of neuroinflammation and chronic pain. The above-mentioned immune mediators can act on their receptors on neurons to regulate neuronal activities and pain sensitivity. Notably, IL-1β can modulate both excitatory and inhibitory synaptic transmission (excitatory and inhibitory postsynaptic currents, EPSC and IPSC) in the spinal cord pain circuit to promote central sensitization. Painful insults also activate Toll-like receptors in nociceptors and glial cells to drive neuroinflammation and chronic pain. Matrix metalloproteases (MMP-2 and MMP-9) are upregulated after painful insults and critically contribute to glial activation and neuroinflammation in chronic pain.

in chronic pain conditions in both animals[88] and patients.[89] TGF-β1, released from most immune cells and platelets, potently inhibits neuropathic pain and suppresses spinal cord glial activation and neuroinflammation after nerve injury in rodents.[90,91] TGF-β1 plays a non-canonical role in rapid and direct neuromodulation: within minutes it activates TGF-β1 receptors (TGFBR1) on neurons, normalizing nerve injury-induced DRG neuronal hyperexcitability and spinal cord synaptic plasticity.[90]

Matrix Metalloproteases (MMPs)

Accumulating evidence suggests an active role of proteases, such as matrix metalloproteases (MMPs), in neuroinflammation and the pathogenesis of chronic pain[70,92] (Figure 16.1). Among a large family of MMPs, the gelatinases MMP-2 and MMP-9 have been implicated in the development and maintenance of neuropathic pain in mice.[93] Nerve injury induces a rapid but transient upregulation in MMP-9 expression and activity in DRG neurons with axonal injury. Notably, secreted MMP-9 is sufficient and required to activate microglia, leading to early-phase neuropathic pain through p38 phosphorylation in spinal microglia.[94–96] In contrast to the rapid induction of MMP-9, nerve injury produces delayed but persistent MMP-2 production in glial cells, leading to late-phase neuropathic pain mediated by astrocyte activation.[94] MMP-9 and MMP-2 participate in IL-1β cleavage/activation and signaling in neuropathic pain.[94] To control tissue damage by MMPs, humans and animals also produce endogenous tissue inhibitors of MMPs (TIMP), with relative selectivity of TIMP-1 for MMP-9 and TIMP-2 for MMP-2. TIMPs are potent suppressants of neuropathic pain: TIMP-1 and TIMP-2 attenuate early-phase and late-phase neuropathic pain, respectively, in mice.[94] Conversely, knockout mice lacking TIMP-1 displayed rapid onset of thermal and mechanical hyperalgesia after injury.[97] MMPs are also implicated in clinical pain. Like MMP-9, TIMP-1 is an injury marker and rapidly induced in neurons and glial cells after painful insults[98] Human genetic pathway analysis revealed a major role for extracellular matrix organization and MMP-9 in patients with inflammatory and neuropathic pain.[99] Pharmaceutical development of small molecule inhibitors of MMPs for treating inflammation and cancer has been attempted, though with limited success, because of liver toxicity and lack of specificity.[93,100] Through functional selection, a highly selective monoclonal antibody against MMP-9 was recently developed, which shows efficacy in a mouse model of chemotherapy-induced neuropathic pain.[100]

Resolvins, SPMs, and Resolution of Pain

Resolution of acute inflammation is an active process that requires the production of specialized pro-resolving mediators (SPMs).[101] Thus SPMs are produced during the resolution phase of inflammation, including sham surgery, a resolution condition associated with acute inflammation and acute pain in mice.[102] A production failure in SPMs could impair inflammation resolution resulting in a transition from acute inflammation to chronic inflammation.[101,103] SPMs consist of several different families, such as resolvins, maresins, and protectins derived from the omega-3 unsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[101] In different mouse models of inflammation, SPMs demonstrate potent anti-inflammation and pro-resolution actions.[104] Strikingly, SPMs also produce powerful antinociceptive and antihyperalgesia in rodent models of inflammatory pain, neuropathic pain, and cancer pain.[105] For example, resolvins D1 and E1 (RvD1 and RvE1) inhibit inflammatory pain in mice at a dose that is 100-fold lower than morphine,[106] and neuroprotectin D1 (NPD1) reduces neuropathic pain at a dose that is 500-fold lower than gabapentin.[107] SPMs control pain via both immunomodulation and neuromodulation[101,106] through acting on distinct GPCRs to regulate the resolution of inflammation.[101] GPR37 is a recently identified receptor for NPD1 and contributes to the resolution of inflammatory pain, as inflammatory pain fails to resolve in mice lacking GPR37.[108]

Sex Dimorphism in Immune Regulation of Pain

Recent pre-clinical studies have demonstrated sex dimorphism in neuroinflammation regulation of pain.[109] For example, spinal microglia, TLR4, P2X4, and p38 MAP kinase regulate inflammatory and neuropathic pain in male animals,[110–113] whereas T-cell signaling appears more critical in female animals.[110] Sex differences in peripheral immune regulation of pain have also been revealed. For example, macrophage-derived TLR9 regulates chemotherapy-induced peripheral neuropathy related mechanical allodynia in male mice.[114] Thus it is important to test neuroimmune-based pain therapeutics in both sexes.

Targeting Neuroimmune Mechanisms by Emerging Regenerative Pain Medicine

Among the emerging therapies in pain management, the use of biologics has shown promise and provided new insights into the neurobiologic mechanisms of pain.[115] Regenerative pain medicine seeks to harness the body's own reparative capacity and is a fast-growing field within pain medicine.[115] Current biologic therapies make use of several general categories of biologics: cellular products such as mesenchymal stem cells (MSC) derived from the bone marrow, adipose tissue, and umbilical cord, and blood-derived products such as platelet rich plasma (PRP) and autologous conditioned serum (ACS).[115] This approach may reduce pain as a symptom and modify disease processes in animals and humans. Although multiple cellular and molecular mechanisms may be at play, neuroimmune modulation by regenerative medicine has emerged as the main mechanism underlying pain relief.

Cell Therapy and Regenerative Approaches in Pre-Clinical Studies

Several lines of pre-clinical studies have demonstrated sustained pain relief by MSCs or bone marrow stem cells (BMSCs) via neuroimmune modulation.[116] Single intravenous or local injection of rat BMSCs reversed mechanical allodynia in rats after tendon injury for several months involving monocyte activation.[117,118] Intrathecal administration of BMSCs via lumbar puncture results in a long-term relief of neuropathic pain after nerve injury.[90] Visualization of dye-labeled BMSCs showed migration to the DRG and spinal cord meninges, where they survived for up to 3 months after intrathecal injection. Intriguingly, neuroimmune interaction guides migration and targeting of BMSCs. After a nerve ligation injury, injured DRG neurons upregulated CXCL12, a chemotactic signal that guides BMSCs to damaged DRGs via a CXCR4/CXCL12 homing mechanism.[90] Furthermore, secretion of the anti-inflammatory cytokine TGF-β1 is responsible for conferring the potent pain relief of the intrathecally injected BMSCs.

Intrathecal administration of anti-TGF-β1 neutralizing antibody selectively reversed the analgesic effect conferred by intrathecal BMSC treatment. Intrathecal BMSCs also control the nerve injury-induced neuroinflammation in the spinal cord, as revealed by microglia and astrocyte activation and increased expression of IL-1β, IL-6, and TNF.[90] It was also shown that intravenous or intrathecal application of MSCs could prevent and reverse opioid-induced tolerance and hyperalgesia and inhibit chronic opioid-induced glial activation in the spinal cord.[119] Intrathecal injection of exosomes, collected from human umbilical cord MSCs, relieves neuropathic pain in rats, by inhibiting nerve injury-induced neuroinflammation.[120] Additionally, neurogenesis of inhibitory neurons has been used for regenerative pain medicine. After spinal transplantation, embryonic cortical GABAergic interneuron precursors from the medial ganglionic eminence could generate inhibitory neurons that can integrate into nociceptive circuits and alleviate neuropathic pain.[121]

Cell Therapy and Blood-Derived Products in Clinical Studies

Cell therapy: Several clinical studies have shown long-term benefits of cell therapy in patients with low back pain. In a prospective, open-label, non-randomized, and single arm study, 26 patients with moderate to severe discogenic low back pain received an injection of autologous bone marrow concentrate into the nucleus pulposus of injured lumbar discs. After 36 months, 20 patients had 71% improvement in Oswestry Disability Index and 70% improvement in visual analog scale scores and no adverse events were noted from the treatment.[122] In another study, 33 patients were treated for degenerative disk disease with a single intradiscal injection of cultured autologous bone marrow mesenchymal stem cells (BM-MSCs). Numeric pain rating scale values were significantly changed at 3, 36, 48, 60, and 72 months post-treatment. No serious adverse effects were associated with the procedure. Twenty of treated patients underwent MRI studies with 85% reporting reduction in disc bulge size.[123] Adipose tissue-derived MSCs also offered a therapeutic option for chronic pain because of their immunomodulatory functions. A single arm phase I clinical trial showed not only safety and tolerability but also relief of low back pain after a single intradiscal injection of autologous adipose tissue-derived MSCs.[124]

Platelet rich serum (PRP): The past decade has seen a substantial increase in using PRP to treat musculoskeletal conditions.[115,125] PRP contains multiple growth factors, such as platelet-derived growth factors, α-granule-based growth factor, TGF-β, and hepatocyte growth factor. TGF-β inhibits inflammation and promotes chondrocyte activity and cartilage growth.[89] PRP-based factors reduced proinflammatory cytokines[126] and increased collagen and proteoglycan production *in vitro*.[127] However, PRP provides limited contribution to the radiographic restoration of cartilage in humans.[128] Randomized PRP-based clinical trials support its functional benefits in treating patients with knee osteoarthritis.[129,130]

ACS. ACS is another blood-derived product for regenerative medicine, boosting the levels of IL-1Ra, an inhibitor of cytokine IL-1 receptor and a cartilage-protective cytokine.[115] Whole blood, in proper incubation conditions, produces IL-1Ra and anti-inflammatory cytokines TGF-β1, IL-4, and IL-10, and extracellular vesicles such as exosomes.[115] ACS was shown to reduce both pain and joint damage in arthritis.[131] A randomized, blinded trial on 376 participants revealed superior outcomes of ACS over intra-articular hyaluronan or placebo, and the beneficial effects of ACS lasted for more than 104 weeks.[132]

Targeting Neuroimmune Mechanism by Neuromodulation

In the following sections, we discuss neuromodulation with a specific focus on SCS and VNS. A unifying theme, regulation of neuroimmune interactions, is a key element of these therapies for pain control.

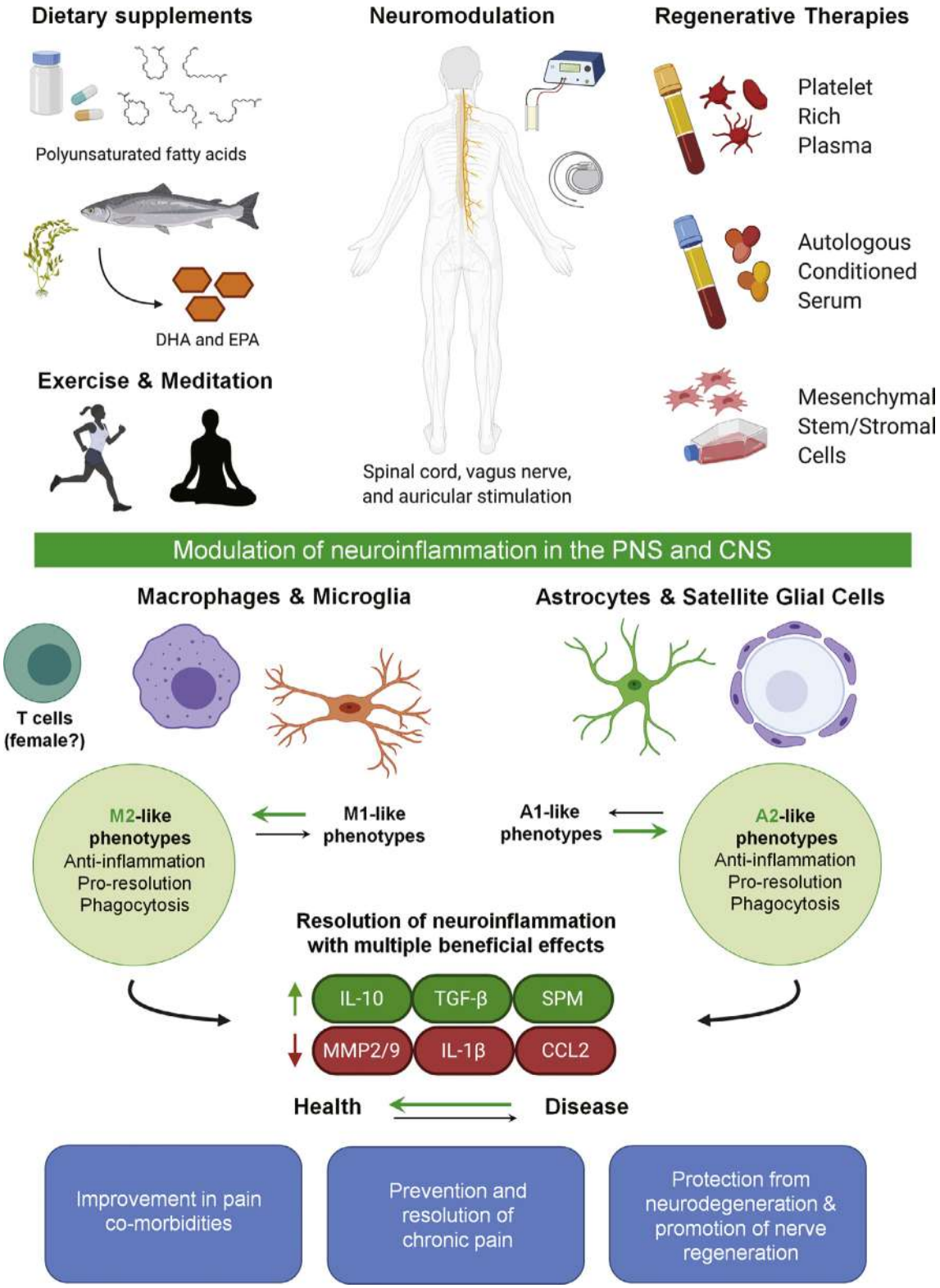
Neuromodulation via SCS

Several new SCS modalities have been developed and investigated in adequately powered and randomized trials. For example, high frequency (10 kHz, HF-10) stimulation has been shown to achieve ≥50% pain reduction of low back pain and leg pain in more than 80% of patients with failed back pain syndrome, compared to 44% for back pain and 55% for leg pain with conventional low frequency stimulation in a multicenter randomized comparative trial.[35] This superiority is maintained in one year and two year follow-ups.[133]

A novel SCS system was developed to continuously monitor evoked compound action potentials (ECAPs) in the dorsal column in response to SCS in patients.[42] These ECAPs are used to optimize programming and deliver closed-loop SCS by adjusting the stimulation current to maintain activation within a patient's therapeutic window. Closed-loop SCS was recently compared with conventional open-loop SCS in a multicenter randomized trial that demonstrates that more than 80% of patients with chronic, intractable pain of the back and legs achieved ≥50% pain reduction in the closed-loop group, versus 61% in the open-loop group.[42,134] It is noteworthy that the study enrolled patients with or without failed back surgery, suggesting that this technology may be applicable to patients without previous back surgery.

A few other modalities of SCS were investigated. Burst stimulation appears to be superior to tonic stimulation.[37] High density stimulation may provide better pain relief in patients who failed conventional SCS for failed back surgery syndrome, CRPS, or neuropathic pain.[39] Differential target multiplexed programming has also shown promise in improving outcomes in a difficult-to-treat population of patients in a recent study.[41]

Several frameworks have been put forward to elucidate the mechanisms of action of SCS.[135–137] The gate control theory, first described by Melzack and Wall in 1965,[53] proposes that non-painful sensory input, via large-diameter sensory fibers, closes the "gates" in the spinal cord dorsal horn laminae, thereby preventing transmission of painful input, via small-diameter fibers. Thus the patient would experience less pain. However, the true mechanisms of neuromodulation are much more complex and remain to be determined. The gate control theory cannot explain the efficacy of HF-10 SCS in the absence of evidence of large fiber activation in this paresthesia-free mode of stimulation. Postulated mechanisms of action for pain relief with high frequency stimulation include axonal conduction block, desynchronization of axonal activity, and glial-neuronal interactions.[40] However, blocking or desynchronizing axonal transmission by HF10 was not supported by experiments in animals or with computational approaches.[137] Pre-clinical and human mechanistic studies suggest that many neuromodulatory techniques likely modulate the conduction, transmission, and perception of pain signals,[137] as well as processes



• **Figure 16.2** Schematic illustration of neuroimmune modulation by therapies such as regenerative therapies (platelet rich plasma, ACS, mesenchymal stem/stromal cells), dietary supplements (polyunsaturated fatty acids, including fish oil DHA and EPA), neuromodulation (spinal cord stimulation and VNS, and auricular stimulation), and exercise and meditation. These therapies can control neuroinflammation in the peripheral nervous system (PNS) and central nervous system (CNS) by downregulation of proinflammatory mediators (e.g. matrix metalloproteases [MMP] -2/-9, interleukin [IL] IL-1β, and CCL2) and upregulations of anti-inflammatory mediators (IL-10, transforming growth factor [TGF] -β) and pro-resolving mediators (SPMs). These therapies could change the activation and phenotypes of immune cells and glial cells, such as M1 and M2-like phenotypes of macrophages and microglia and A1 and A2 phenotypes of astrocytes and satellite glial cells. M2- and A2-like phenotypes are associated with anti-inflammation, pro-resolution, and pro-phagocytosis benefits. These health benefits will help prevent and resolve chronic pain, protect against neurodegeneration, promote regeneration, and improve chronic pain-associated comorbidities (e.g. cognitive impairment and depression). Recent pre-clinical studies have revealed distinct sex dimorphism in microglial and T-cell regulation in chronic pain, which requires validation in clinical studies.

involving non-neuronal cells in the spinal cord that contribute to central sensitization and chronification of pain.[40] A significant finding is that electrical stimulation can profoundly modulate the immune system in the central and peripheral nervous systems that constitute the essential substrate of central and peripheral sensitizations of pain. Accumulating evidence from pre-clinical studies shows that SCS modulates glial activation in rodent models of neuropathic pain.[138] A recent study shows that the expression of glia-related genes such as Tlr2, Cxcl16, Cd68, Gfap, Ccl2, and Itgam was associated with the effects of SCS on a neuroinflammatory state induced by nerve injury in rats.[40] However, the detailed signaling mechanisms underlying this neuroimmune modulation are largely unknown.

Neuromodulation via Vagus Nerve Stimulation (VNS)

VNS has been tested to treat patients with fibromyalgia, pelvic pain, migraine, and cluster headaches.[105,139] Inflammation in the cavernous sinus and tributary veins might be responsible for cluster headaches.[140] In a randomized sham-controlled study, noninvasive VNS provided significant and sustained benefits for episodic cluster headaches without showing efficacy for chronic cluster headaches.[46] It will be of great interest to investigate how VNS activates afferent inputs to suppress inflammation and relieve episodic cluster headaches. Notably, the human vagus nerve contains SPMs (e.g. resolvin E1 and D5, protectin D1, and maresin 1), and electrical stimulation of the vagus nerve *in vitro* further increased SPM production but decreased proinflammatory prostaglandins and leukotrienes.[47,141] VNS has also been shown to regulate basal pain sensitivity in healthy volunteers. Both mechanically evoked pain and noxious tonic heat-induced temporal summation were suppressed by percutaneous VNS.[142]

Pre-clinical studies have provided new insights into inflammation and pain control by VNS. Stimulation of the right vagal nerve trunk was shown to produce antinociception.[143] The "inflammatory reflex" hypothesis proposed a vagus nerve-mediated neural circuit that is capable of providing information in real-time to the brain about the body's inflammatory status. This vagus nerve-mediated inflammatory reflex enables a rapid neural regulation of inflammation.[144] Interestingly, vagotomy (transection of the vagus nerve) reduced local production of SPMs in exudates and impaired the resolution of inflammation.[145] Auricular VNS via electroacupuncture was shown to reduce neuropathic pain in a mouse model of paclitaxel-induced neuropathy. Auricular VNS treatment effectively alleviated neuropathic pain and increased SPM levels (resolvin D1/RvD1) in mice.[105] Several SPMs, including RvD1, are sufficient to attenuate mechanical allodynia in mice.[146] Thus VNS may alleviate neuropathic pain via the production of SPMs (RvD1, Figure 16.2).

Precision Pain Medicine

Precision medicine was initially proposed for cancer treatments, given the well-recognized cancer diversity and individual variability in anti-cancer drug therapy. While a "one-drug-fits-all" model could be mechanism-based, it ignores individual differences in genetic and environmental factors. Precision medicine is an approach to "personalized medicine" that proposes the customization of health care so that medical treatments are specifically tailored to the unique needs of each individual patient. Precision medicine is based on the context of the genetic makeup and other molecular or cellular properties of each patient, and, therefore, diagnostic testing could be employed for selecting appropriate and optimal therapies.

The term "precision pain medicine" has been loosely used in different places to mean different things. For example, it is used by many clinics to mean anatomic precision when performing nerve blocks under the guidance of advanced imaging technologies or to mean disease-specific interventions, such as "regenerative medicine" to regenerate specific tissue (e.g. joint cartilage) for pain management. While these interventions may be precise, they are not based on each patient's genetic and environmental factors. Thus there is a need to clearly define the concept of "precision pain medicine." Specifically, precision pain medicine has to be based on genomic testing and lifestyle information of each individual patient to achieve personalized treatment.

While clinical applications of precision pain medicine are still in their infancy, specific genes associated with specific pain conditions have been identified. For example, the gain-of-function mutations of the voltage-gated sodium channel subtype Nav1.7 (encoded by *SCN9A* gene) has been associated with inherited erythromelalgia, which is characterized by recurrent attacks of bilateral, symmetrically intense pain accompanied by redness, warmth, and swelling.[147] Pharmacotherapy guided by genomic analysis, molecular modeling, and functional profiling has been shown to attenuate neuropathic pain in patients carrying the Nav1.7 S241T mutation.[148] This finding provides proof-of-principle that, using genomics and molecular modeling, a specific pain medicine can be matched to a particular person's DNA to achieve individualized and effective treatment. This line of work signifies the beginning of a transformation from mechanism-based, trial-and-error practice to precision pain management.

Both nociception and the risk of clinical pain have been associated with Catechol-O-methyltransferase (COMT) genetic variants, which metabolize catecholaminergic neurotransmitters and modulate adrenergic pathway transmission. Genetic variations in COMT isoforms may contribute to individual variability in pain phenotypes.[149,150] COMT inhibition is associated with neuroinflammation and pain hypersensitivity in rodents.[151] Genetic analysis also suggests that epidermal growth factor (EGF) receptor modulates human nociception via the PI3 kinase and MMP-9 pathway.[152]

Human genetic studies further revealed an association between GTP cyclohydrolase 1 (GCH1) polymorphisms and reduced pain in patients. GCH1 is involved in the production of monoamine neurotransmitters, the generation of nitric oxide, and the expression of the rate-limiting enzyme for the production of tetrahydrobiopterin (BH4).[19] The contribution of the GCH1-BH4 pathway to neuropathic pain is validated in a mouse model of neuropathic pain after nerve injury, which causes GCH1 upregulation in sensory neurons leading to increased BH4 synthesis.[19] Furthermore, BH4 regulates T-cell proliferation in mouse and human tissues and contributes to autoimmunity.[153] Thus the GCH1-BH4 pathway may control pain via both neural and immune regulations.

There are other examples of specific genes associated with specific pain conditions. Evidence exists to support an association of the TWIK-related spinal cord potassium (K^+) channel (TRESK) gene,[154] and the methylene tetrahydrofolate reductase (MTHFR) gene in migraine pain.[155,156] Furthermore, three causative genes have been identified in familial hemiplegic migraine families: CACNA1A, ATP1A2, and SCNA1A *encoding the* alpha 1A subunit of voltage-dependent calcium channel type P/Q (MIM601011),

the alpha 2 subunit of Na+/K+–ATPase (MIM182340), and the α subunit of the neuronal voltage-gated Na+ channel *respectively*. Recently, several mutations in KCNK18 have also been found as causative factors in migraine development.[157]

Pharmacogenetics considers a patient's unique genetic information and allows for the prediction of an individual's response to medication. Pharmacogenomic testing is increasingly recognized in pain management to identify individual differences in the perception of pain and sensitivity to drugs based on genetic markers. Streamlining relevant polymorphisms of genes encoding receptors, transporters, and drug-metabolizing enzymes influencing the pain phenotype can guide personalized pain management. While recognizing the challenges and barriers in clinical adoption of pharmacogenomic testing, recent progress in this emerging field has shown enormous promise toward the development of precision pain medicine.[158]

Conclusion and Perspective

It has been estimated that one in five Americans is affected by chronic pain, with an annual cost of over 600 billion dollars. Given the rapid increase of an aging population, the prevalence of chronic pain and pain-related disability is also rising. There is a critical and urgent need to develop new strategies to address the dual crises of chronic pain and the opioid epidemic in the United States. Mechanism-based and precision pain medicine represents the best and most promising approach to safe, efficacious, and cost-effective care of patients with chronic pain.

In this chapter, we reviewed state-of-the-art, mechanism-based treatments. We discussed the current treatments that are partially effective for a proportion of patients with appropriate indications (Table 16.1). We also discussed treatments that are under development but show limited success (Table 16.2). We highlighted biologics, including recently approved therapies such as monoclonal antibodies against CGRP and CGRP receptor that have shown great success in treating migraine headaches, as well as emerging therapies including cell therapies (mesenchymal stromal cells/MSCs) and blood-derived products (PRP, ACS) that have shown long-term benefits with support from a body of literature.

As a main focus of this chapter, we highlighted neuroimmune modulation as a key mechanism of chronic pain (Figure 16.1) and a promising therapeutic target of current treatment (neuromodulation with SCS and VNS and emerging therapies MSCs, PRP, and ACS). Notably, SPMs exert potent analgesic actions while simultaneously promoting inflammation resolution in rodents. SPMs may also serve as a biomarker of chronic pain with reduced production and a biomarker for effective treatment.[102,159,160] Interestingly, a battery of effective treatments such as neuromodulation and regenerative medicine may alleviate pain through inducing SPM production. Dietary supplements such as fish oil may produce beneficial effects by conversion to SPMs. The Food and Drug Administration (FDA) recently approved an omega-3 fish oil-based medication, Vascepa (4 mg/day), to reduce the risk of cardiovascular disease. A randomized clinical trial shows that dietary omega-3 fatty acids could alleviate headaches and increase SPM levels.[160,161] It will also be of great interest to study the synergistic effect between a healthy diet, exercise,[162] and neuromodulation for the resolution of pain through regulation of neuroinflammation (Figure 16.2).

The significance of genetic predisposition has been increasingly recognized in determining the vast individual variability in pain sensitivity, responses to pain, transition from acute to chronic pain, and susceptibility and sensitivity to therapies. The current mechanism-based therapies fail to consider the genomic and environmental factors, leading to large individual variations in clinical outcomes (efficacy and adverse events) in response to the same treatments for the same indications. The extraordinarily high numbers-need-to-treat for most pharmacologic agents to treat neuropathic pain,[163] illustrate the eminent deficiency of current mechanism-based pain therapies. Precision pain medicine based on genomic testing and streamlining of relevant polymorphisms of genes encoding receptors, transporters, and drug-metabolizing enzymes influencing the pain phenotype represents a future direction of personalized pain management. Environmental factors, including lifestyle, cognitive-behavioral patterns, and social determinants, are also indispensable elements of precision pain medicine. Only when individual genetic, psychosocial, and environmental factors are accounted for in applying mechanism-guided and evidence-based therapies can we genuinely practice patient-centered and individualized precision pain medicine and fundamentally improve the efficacy, safety, and cost-effectiveness of patient care.

Key Points

- Chronic pain is prevalent and has a high impact on public health and individual lives. Effective treatment of pain depends on adequate assessment, accurate diagnosis, and mechanistic understanding of the complex causes of pain for each patient.
- As we deepen our understanding of pain at cellular and molecular levels, therapeutic targets and strategies are expanding and becoming more mechanism-based, particularly in the field of neuroimmune modulation, regenerative pain medicine, and electrical neuromodulation.
- Current mechanism-based therapies include state-of-the-art approaches to modulating the transduction, conduction, transmission, perception, and adaptation of pain through pharmacologic, interventional, surgical, and physical/psychological/behavioral treatments of specific molecular and cellular targets and neural networks.
- Pharmacologic therapy achieves analgesic effects through a wide range of mechanisms by the use of local anesthetics, NSAIDs, anti-depressants, anti-convulsants, muscle relaxants, and opioids, among other drugs (Table 16.1). Besides these clinically used agents, new mechanism-informed agents are being investigated or developed (Table 16.2).
- Interventional therapy is used to block nociceptive conduction through nerve blocks and/or neural ablation through radiofrequency ablation, cryoneurolysis, chemoneurolysis, or mechanical compression to provide a variable duration of pain relief. Surgical procedures are often required to relieve pain by decompressing specific nerves that are compressed, entrapped, or injured.
- The roles of physical, cognitive, and behavioral therapies are increasingly recognized in pain management, even though the mechanisms for most of these therapies are complex and remain to be elucidated.
- The investigation and appreciation of neuroimmune modulation of pain has revealed new and emerging therapeutic

targets. Pathogenesis of chronic pain is highly related to neuroinflammation mediated by the interaction between neurons, glial cells, and immune cells in the peripheral and central nervous systems through proinflammatory cytokines, chemokines, and matrix metalloproteases and anti-inflammatory cytokines, chemokines, and specialized pro-resolving mediators. The latter are key mediators in an active process of resolution of inflammation and pain.

- Targeting neuroimmune mechanisms of chronic pain by biologics and regenerative medicine has shown promise in pre-clinical and clinical investigations. For example, clinical applications of biologics such as monoclonal antibodies against CGRP or its receptor have changed the landscape of migraine headache management. MSCs have shown promise in mitigating degenerative joint disease (including degenerative disc disease), neuropathic pain, and opioid tolerance. Both PRP and ACS have been shown to provide significant pain relief and functional benefit in patients with knee osteoarthritis in randomized clinical trials through neuroimmune interactions.
- Neuromodulation through modalities such as SCS, dorsal root ganglion stimulation, and VNS has been shown to regulate neuroimmune interaction as a key element of long-term pain relief. Many technological advances in neuromodulation have been made in recent years to significantly improve clinical outcomes in several high impact randomized clinical trials. The potential signaling pathways underlying glial cell activation and neuroimmune interactions have been implicated in pre-clinical studies.
- Any treatment has to be tailored to the unique needs of each individual patient. Precision medicine is based on genomic testing and psychosocial information of each patient to achieve personalized treatment. While clinical applications of precision pain medicine are still in their infancy, multiple specific genes associated with specific pain conditions have been identified and pharmacotherapy guided by genomic analysis, molecular modeling, and functional profiling has shown promising outcomes in pain relief. Subgroup analyses examining physical and psychosocial factors should inform the development of treatments and the matching of treatments to unique characteristics of patients.

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17

Placebo and Nocebo Effects in Clinical Trials and Clinical Practice

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The Magnitude of Placebo Analgesia

Pain is by far the most studied placebo condition, and a large number of studies on the placebo effect have been performed in experimentally induced pain in healthy subjects or patients experiencing a painful condition. There are at least two explanations for this finding. First, pain is a subjective experience that undergoes psychological and social modulation more than any other condition. The fine tuning of the global pain experience by many psychosocial factors makes pain an excellent model for identifying and understanding the placebo effect. The second explanation stems from the influential work of Beecher in the 1950s. In fact, in 1955, Beecher reviewed 15 controlled trials involving 1802 patients.[1] Defining positive outcomes as the "percent satisfactorily relieved by placebo," Beecher reported effect sizes ranging from 26% to 58%, with an average of 35%. The notion that about one-third of patients respond to a placebo has since permeated medical texts and teachings, even though this work has been criticized on methodological grounds.[2,3] In fact, a real figure of Beecher's study was that the magnitude of placebo analgesia might range from no responses to large responses. For example, Levine et al.[4] found that 39% of patients had an analgesic response to placebo treatment, and in a study of ischemic arm pain in normal volunteers, Benedetti[5] found that 26.9% of them responded to a placebo analgesic compared to a no treatment control group. Another study involving cutaneous heating of the left hand found that 56% of subjects responded to placebo treatment compared to the no treatment controls.[6]

Assessing the magnitude of the placebo analgesic effect is not an easy task, as the experimental conditions and the psychological state of the subjects change across different studies. Several studies measured the average change in pain experienced by those receiving placebo and compared this figure to the average change in the no treatment group, and found that the magnitude of the placebo analgesic effect is about two out of ten units on a visual analog (VAS) or numeric rating scale (NRS).[7–10] In studies where the known placebo responders in a group are separated for analysis, the average magnitude of analgesia has been found, not surprisingly, to be significantly greater. For example, when Benedetti (1996)[5] looked only at responders, he found an average placebo analgesia magnitude of five units on the ten unit NRS. This is similar to a postoperative dental study that found a 3.3 cm (out of ten) lower mean post-treatment VAS score for placebo responders compared to nonresponders.[11]

The experimental manipulation used to induce placebo analgesia played a fundamental role in the magnitude of the response. Verbal suggestions that induce certain expectations of analgesia induce larger placebo analgesic responses than those that induce uncertain expectations. This is illustrated by a study carried out in a clinical setting that investigated the differences between the double-blind and deceptive paradigms.[12] Postoperative patients were treated with buprenorphine, on request, for three consecutive days consecutively and with a basal infusion of saline solution. However, the symbolic meaning of this saline basal infusion was varied in three different groups of patients: the first group (natural history or no-treatment group) was told nothing; the second group was told that the infusion was either a potent analgesic or a placebo (classic double-blind administration); and the third was told that the infusion was a potent painkiller (deceptive administration). The placebo effect of the infusion was measured by recording the doses of buprenorphine requested over the three day treatment. It is important to stress once again that the double-blind group received uncertain verbal instructions ("It can be either a placebo or a painkiller. Thus, we are not certain that the pain will subside"), whereas the deceptive administration group received certain instructions ('It is a painkiller. Thus the pain will subside soon. Compared to the natural history group, a 20.8% decrease in buprenorphine intake was observed with double-blind administration. An even greater decrease (33.8%) was observed in the deceptive administration group. It is important to point out that the time course of pain was the same in all three groups over the three day treatment period. The same analgesic effect was observed with different doses of buprenorphine. Thus subtle differences in the verbal context of the patient may have a significant impact on the magnitude of the response. Verne et al.[13] and Vase et al.[14] conducted two similar studies in which patients with irritable bowel syndrome (IBS) were exposed to rectal distension using a balloon barostat, a type of visceral stimulation that simulates their clinical pain. They tested patients with untreated natural history (baseline), rectal placebo, and rectal lidocaine. Pain was rated immediately after each stimulus in each condition. The first study was conducted as a double-blind crossover clinical trial, so patients were given an informed consent form stating that they "may receive an active pain reducing medication or an inert placebo agent."[13] In this study, there was a significant pain-relieving effect of rectal lidocaine compared to rectal placebo, and a significant pain-relieving effect of rectal placebo compared

to the no-treatment condition. In the second study, at the onset of each treatment condition (rectal placebo, rectal lidocaine), patients were told, "The agent you have just been given is known to significantly reduce pain in some patients."[14] A much larger placebo analgesic effect was found, which did not significantly differ from that of rectal lidocaine. These two studies show that adding an overt suggestion for pain relief can increase placebo analgesia to a magnitude that matches that of an active agent.

Experience can also influence the magnitude of placebo analgesia. In one study, the intensity of painful stimulation was reduced surreptitiously after placebo administration, leading subjects to believe that an analgesic treatment was effective.[15] This procedure induced strong placebo responses after minutes, and these responses, albeit reduced, lasted up to four to seven days. This procedure was repeated four–seven days after totally ineffective analgesic treatment in the second group of participants. The placebo responses were markedly reduced compared to those in the first group. These results emphasize that the placebo effect may represent a learning phenomenon involving several factors and may explain the large variability in the magnitude of placebo responses among studies. The number of learning trials carried out in a conditioning procedure is also related to the subsequent magnitude of the placebo effects.[16] Learning processes are not only important for psychophysical measurements such as pain rating, but also affect neurophysiologic parameters, such as laser-evoked potentials.[17] Furthermore, and Colloca and Benedetti[18] showed that social observational learning, whereby placebo responses can be learned by merely observing others, plays an important role.

As the magnitude of placebo analgesia depends on many factors, and learning is crucial in several circumstances, the clinical trial setting does not seem to be the best model for studying the placebo analgesic response. In the study by Hrobjartsson and Goetzsche,[19] a meta-analysis was performed of 130 trials in which placebo and no treatment groups were identified in different pathologic conditions. No difference was found between the two groups for many conditions, but a significant placebo effect was found for pain in 29 clinical trials, indicating that pain is one of the best conditions where the placebo effect is present and can be studied. To further investigate the placebo effect in analgesic studies only, Vase et al.[20] conducted two meta-analyses: one covered 23 of the 29 clinical trials included in Hrobjartsson and Goetzsche's meta-analysis,[19] and the other covered only 14 studies investigating the mechanisms of placebo analgesia. They found that the magnitude of placebo analgesic effects was higher in studies that investigated placebo analgesic mechanisms than in clinical trials in which the placebo was used only as a control condition.

Modulation of pain perception by placebos critically depends on expectation, as shown in many studies[21–23]; for example, Price et al.[22] applied placebo creams and graded levels of heat stimulation on three adjacent cutaneous regions of the forearm, suggesting that cream A was a strong analgesic, cream B was a weak analgesic, and cream C was a control agent. Immediately after these conditioning trials, participants rated their expected pain levels for the placebo test trials, wherein the stimulus intensity was the same for all three regions. The conditioning trials led to graded levels of expected pain (C ≥ B ≥ A) for the three creams and graded magnitudes of actual pain (C ≥ B ≥ A) when tested during placebo test trials. Thus the magnitude of placebo analgesia could be graded across three adjacent skin areas, demonstrating a high degree of somatotopic specificity for placebo analgesia. Expected pain levels accounted for 25% to 36% of the variance in post-manipulation pain ratings. In another study,[24] one group of subjects was pharmacologically pre-conditioned with ketorolac (a non-opioid analgesic) for two days in a row. The ketorolac was then replaced with a placebo on the third day, along with verbal suggestions for analgesia. This procedure induces a strong placebo analgesic response. To determine whether this response was because of pharmacologic pre-conditioning, the second group of subjects was also pre-conditioned with ketorolac, but the placebo was administered on the third day along with verbal suggestions that the drug was a hyperalgesic agent. These verbal instructions were sufficient not only to completely block the placebo analgesia but also to produce hyperalgesia. This study clearly shows that placebo analgesia depends on the expectation of a decrease in pain, even when analgesic preconditioning is performed.

The expectation of analgesia can also make a big difference in clinical trials, so the patient's expectations must be considered whenever a clinical trial is conducted. In one clinical trial, real acupuncture was compared with sham acupuncture. Patients were asked which group they believed they belonged to (either placebo or real treatment). Patients who believed they belonged to the real treatment group experienced larger clinical improvement than those who believed they belonged to the placebo group.[25] while in another clinical trial, patients with higher expectations about acupuncture experienced greater clinical benefits than those with lower expectations, regardless of their allocation to real or sham groups.[26] It did not matter whether the patients actually received the real or the sham procedure—what mattered was whether they believed in acupuncture and expected a benefit from it.

Some of the best evidence underscoring the crucial role of positive and negative expectations in the outcome of analgesic treatments is the decreased effectiveness of hidden treatments. This involves giving an analgesic covertly (unexpectedly), so the patient is unaware a drug is being injected; the outcome following the hidden (unexpected) administration is compared with that following an open (expected) administration.[27,28] Careful analysis of the differences between open (expected) and hidden (unexpected) injections in postoperative settings was performed for five widely used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizole).[10,27]

That the hidden administration of a pharmacologic agent is less effective than an open one may suggest a different pharmacodynamic action of the drug in the absence of expectations. Although we do not know whether expectations and therapeutic rituals can modify a receptor to change the drug-receptor binding properties, to the best of our knowledge, this mechanism seems unlikely. The global effect of a drug derives from its specific pharmacodynamic action plus the psychological (placebo) effect coming from the very act of its administration. A recent study suggested that these two components operate independently from each other.[29]

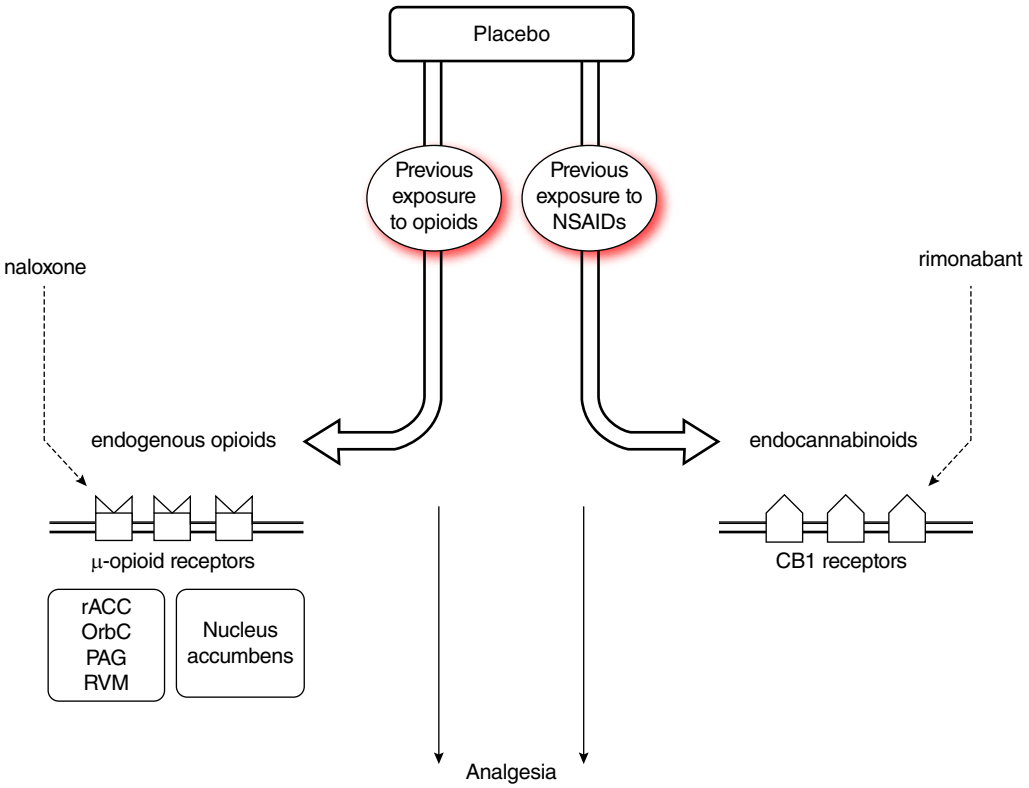
Expectations may also be associated with other factors, such as the desire for relief and reduction of anxiety. In other words, placebo phenomena occur within the context of emotional regulation, and symptoms should be influenced by desire, expectation, and intensity of emotional feeling.[23] Desire and expectation interact and underlie common human emotions like sadness, anxiety, and relief,[30] thus in the context of analgesic studies, it is quite plausible that patients and study participants have some degree of desire to avoid, terminate, or reduce evoked or ongoing pain.

Placebo-Induced Activation of Endogenous Painkillers (Fig. 17.1)

Placebo administration has been found to activate endogenous mechanisms of analgesia, and the placebo effect represents one of the most interesting models for understanding when and how these mechanisms are activated.[31] The organization of the endogenous antinociceptive systems is complex. Thanks to the pioneering work on producing analgesia in rats by stimulation of the periaqueductal grey[32] and the discovery of stereospecific binding sites for opioids,[33] endogenous enkephalins[34] in the central nervous system, we know that a complex endogenous network exists, which includes both opioid and non-opioid systems.[35,36]

Most of our knowledge about placebo analgesia is based on the opioid mechanisms. Opioid receptors can be found throughout the brain, brainstem, and spinal cord.[37–41] These receptors may exert analgesic effects through different mechanisms,[42] such as modulation at the spinal level and/or control of cortical and brainstem regions. The modulation of the spinal cord is one of the best described.[40,41] The opioid system in the brainstem consists of different regions, such as the periaqueductal gray, parabrachial nuclei, and the rostral ventromedial medulla.[40,41] Although opioid receptors are less characterized in the cortex, autoradiographic studies indicate high concentrations of opioid receptors in the cingulate cortex and prefrontal cortex,[37–39] and one of the highest levels of opioid receptor binding has been found in the anterior cingulate cortex.[43] Studies performed using positron emission tomography, and the radioactive opioid 11C-diprenorphine confirms previous animal and human autoradiographic findings.[44,45] In addition, opioid receptor agonists, such as remifentanil and fentanyl, have been shown to act on several regions that are known to be involved in pain processing and contain high concentrations of opioid receptors.[6,46]

One of the main problems of this endogenous opioid network is understanding when and how it is involved in analgesic effects. The first study of the biologic mechanisms of placebo analgesia used the opioid antagonist naloxone to block opioid receptors.[11] It was performed in a clinical setting in patients who had undergone extraction of their third molar tooth. The investigators found disruption of placebo analgesia after naloxone administration, which indicates the involvement of endogenous opioid systems in the placebo analgesic effect. Since the publication of the study by Levine et al.[11] attempts have been made to verify and reproduce the findings. For example, by using the experimental pain model of arm ischemia (the tourniquet technique), Grevert et al.[47] found a partial reversal of placebo analgesia by naloxone, thus confirming previous findings. Likewise, Levine and Gordon[8] adopted an elegant experimental design that showed naloxone-reversed placebo analgesia in a clinical situation, namely postoperative pain after extraction of the third molar. However, in 1983, Gracely et al.[7] demonstrated that naloxone might have hyperalgesic effects



• **Figure 17.1** During a placebo procedure, pain perception may be reduced through opioid and/or non-opioid mechanisms. The previous exposure to opioids leads to opioid-mediated placebo analgesia (disrupted by naloxone). The previous exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) leads to cannabinoid-mediated placebo analgesia (disrupted by rimonabant). Endogenous opioids inhibit pain through a descending inhibitory network – involving rostral anterior cingulate cortex (rACC), orbitofrontal cortex (OrbC), periaqueductal gray (PAG), rostral ventromedial medulla (RVM) – and/or other mechanisms. High opioid and dopamine activity in the nucleus accumbens are also involved in placebo analgesia. Little is known about CB1 cannabinoid receptors' localization and activation.

on postoperative pain, thus shedding some doubt on the opioid hypothesis of placebo analgesia.

From 1995 to 1999, a long series of experiments with rigorous experimental designs were performed by Benedetti et al. Many unanswered questions have been clarified during these years, and the role of endogenous opioids in placebo analgesia has been explained. The experimental ischemic arm pain model was used to show that naloxone does not affect this type of pain. Therefore any effect following naloxone administration could be attributed to the blockade of placebo induced opioid activation.[5] At the same time, these investigators tested the effects of a cholecystokinin (CCK)-antagonist, proglumide, on placebo analgesia. Based on the anti-opioid action of CCK, it was hypothesized that blockade of CCK receptors would enhance the opioids released by the placebo. Indeed, it was found that proglumide potentiated the placebo analgesia and presented a novel and indirect way to test the opioid hypothesis.[5,48] More recently, the activation of the CCK type-2 receptors was performed using the agonist pentagastrin, which disrupted placebo responses completely.[49] Therefore the activation of the CCK type-2 receptors has the same effect as the μ-opioid receptor antagonist naloxone, suggesting that the balance between cholecystokinergic and opioidergic systems is crucial for placebo responsiveness in pain. Therefore one of the most interesting models involves two opposing neurotransmitter systems, opioids and CCK.

Specific placebo analgesic responses can be obtained in different parts of the body.[21,22] It was found that these responses are naloxone reversible.[50] If four noxious stimuli are applied to the hands and feet, and a placebo cream is applied to one hand only, then pain is reduced only on the hand on which the placebo cream had been applied. This highly specific effect is blocked by naloxone, suggesting that the placebo-activated endogenous opioid systems have a precise and somatotopic organization.[50]

Petrovic et al.[6] found that some brain regions in the cerebral cortex and brainstem are affected by both a placebo and the rapidly acting opioid agonist remifentanil, indicating a related mechanism in placebo induced and opioid-induced analgesia. Administration of a placebo induced activation of the rostral anterior cingulate cortex and orbitofrontal cortex. Moreover, there was significant co-variation in activity between the rostral anterior cingulate cortex and the lower pons and medulla, and sub-significant co-variation in activity between the rostral anterior cingulate cortex and the periaqueductal gray. This suggested that the pain modulating circuit of the descending rostral anterior cingulate-periaqueductal gray-rostral ventromedial medulla is involved in placebo analgesia, as previously hypothesized by Fields and Price.[51] The first direct evidence of opioid-mediated placebo analgesia was published in 2005.[52] *In vivo* receptor binding techniques using the radiotracer carfentanil, a μ-opioid agonist, were used to show that a placebo procedure activates μ-opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens. A more detailed account of μ-opioid neurotransmission after placebo administration was carried out in another study that used noxious thermal stimulation.[53]

Placebo treatment affected opioid activity in several opioid-rich regions that play central roles in pain and affect, including the periaqueductal gray, dorsal raphe, nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rostral anterior cingulate, and lateral prefrontal cortex. Opioid activity in many of these regions was correlated with placebo effects in reported pain. Connectivity analyses of individual differences in opioid binding revealed that placebo treatment increased connectivity between the periaqueductal gray and the rostral anterior cingulate cortex and increased functional integration among limbic regions and the prefrontal cortex. Overall, the results suggest that endogenous opioid release in core affective brain regions is an integral part of the mechanism whereby expectations regulate affective and nociceptive circuits.

Our knowledge about the involvement of endogenous opioids in placebo analgesia has increased even more in the past few years. For example, it is now clear that a specific descending pain-modulating network mediates the analgesic effect following placebo administration. Eippert et al.[54] combined naloxone administration with functional magnetic resonance (fMRI) imaging and found that naloxone reduced both behavioral and neural placebo effects as well as placebo induced responses in pain modulatory cortical structures such as the rostral anterior cingulate cortex. A brainstem-specific analysis also found a similar naloxone modulation of placebo induced responses in key structures of the descending pain control system, such as the hypothalamus, periaqueductal gray, and rostral ventromedial medulla. Interestingly, naloxone abolished the placebo-induced coupling between the rostral anterior cingulate cortex and the periaqueductal gray, which predicted both behavioral and neural placebo effects as well as the activation of the rostral ventromedial medulla. The same group found that the activation of this descending system following placebo administration extends to the dorsal horns of the spinal cord, although we do not know whether the spinal effects are mediated by endogenous opioids.[55]

It has long been known that endogenous opioid systems are not the only mechanisms involved in placebo analgesia. One example of non-opioid-mediated placebo responses is represented by previous exposure to a non-opioid drug, such as ketorolac.[56] When ketorolac is administered for two days in a row and then replaced with a placebo on the third day, the placebo analgesic response is not reversed by naloxone, indicating that specific pharmacologic mechanisms are involved in a learned placebo response, depending on the previous exposure to opioid or non-opioid substances. Other examples of placebo analgesic effect that are not mediated by opioids have been described in people with IBS[57] and experimental pain in brain imaging studies.[36] Based on these considerations, Benedetti et al.[58] induced opioid or non-opioid placebo analgesic responses and assessed the effects of the CB1 cannabinoid receptor antagonist rimonabant. Unlike naloxone, rimonabant had no effect on opioid-induced placebo analgesia following morphine pre-conditioning, whereas it completely blocked placebo analgesia following non-opioid pre-conditioning with the nonsteroidal anti-inflammatory drug (NSAID) ketorolac. These findings indicate that the placebo analgesic responses elicited by NSAID conditioning are mediated by CB1 cannabinoid receptors.

Since the involvement of CB1 cannabinoid receptors in placebo analgesia is a recent finding, little is known about their localization and activation. To the best of our knowledge, they are activated following a previous exposure to NSAIDs, which suggests that these drugs, besides the inhibition of cyclooxygenase and prostaglandin synthesis, activate an endocannabinoid pathway.[58] Indeed, non-opioid drugs, such as metamizole, have been found both to inhibit the enzyme cyclooxygenase and to act on the CB1 cannabinoid receptors in rodents.[59] Based on these considerations, a change in the availability of endogenous ligands for CB1 cannabinoid receptors, such as anandamide, should be expected to modulate placebo analgesia in some circumstances. Indeed, Pecina et al.[60] investigated the role of the common, functional missense variant Pro129Thr, of the gene encoding fatty acid amide hydrolase

(FAAH), the major degrading enzyme of endocannabinoids, on psychophysical, dopaminergic, and opioid responses to pain and placebo induced analgesia in humans. FAAH Pro129/Pro129 homozygotes reported higher placebo analgesic responses and more positive affective states immediately and 24 hours after placebo administration. Pro129/Pro129 homozygotes also showed greater placebo induced μ opioid, but not D2/D3 dopaminergic enhancements in neurotransmission in regions known to be involved in placebo effects.

Neuroimaging of Placebo Analgesia (Fig. 17. 1)

Modern brain imaging techniques have been fundamental in the understanding of placebo analgesia, and many brain imaging studies have been carried out to describe the functional neuroanatomy of the placebo analgesic effect[6,52–55,61–65] As described above, the first imaging study of placebo analgesia showed that a subset of brain regions is similarly affected by either a placebo or a μ-opioid agonist.[6] In an fMRI imaging study of experimentally induced pain in healthy participants, Wager et al.[61] found that placebo analgesia was related to decreased neural activity in pain processing areas of the brain. Pain-related neural activity was reduced within the thalamus, anterior insular cortex, and anterior cingulate cortex during the placebo condition compared with the baseline condition. The magnitude of these decreases correlated with reductions in pain ratings. Not only did Wager et al.[61] image the time period of pain as well as the time period of the anticipation of pain. They hypothesized an increase in neural activity within the brain areas involved in expectation. Indeed, they found significant positive correlations between increases in brain activity in the anticipatory period and decreases in pain and pain-related neural activity during stimulation within the placebo condition. The brain regions showing positive correlations during the anticipatory phase included the orbitofrontal cortex, dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and midbrain periaqueductal gray. The dorsolateral prefrontal cortex is a region that has been associated with the representation and maintenance of information needed for cognitive control, consistent with a role in expectation.[66] In contrast, the orbitofrontal cortex is associated with functioning in the evaluative and reward information relevant to the allocation of control, consistent with a role in affective or motivational responses to anticipation of pain.[67] The anterior cingulate cortex is often reported to be involved in placebo analgesia, although some discordant results have been obtained. For example, it was found to have increased activity in a study by Petrovic et al.[6] and decreased activity in a study by Wager et al.[61] which might be explained based on the different experimental settings.

Most brain imaging studies aimed at investigating placebo analgesia have been performed in experimental settings in healthy volunteers. In contrast, Price et al.[62] conducted an fMRI imaging study in which brain activity of IBS patients was measured in response to rectal distension using a balloon barostat. A large placebo effect was produced by suggestions and accompanied by large reductions in neural activity in the thalamus, primary and secondary somatosensory cortices, insula, and anterior cingulate cortex during the period of stimulation. It was accompanied by increases in neural activity in the rostral anterior cingulate cortex, bilateral amygdala, and periaqueductal gray. This study is important and informative, as it shows that placebos act on the brain in a clinically relevant condition in the same way as they do in the experimental setting. Therefore the involvement of key areas in placebo analgesia, such as the anterior cingulate cortex, is not limited to experimental noxious stimuli but also extends to clinical pain. The study by Price et al.[62] is also interesting because reductions in brain activity occurred during the stimulus presentation itself, not just when subjects reported pain. It has been argued that the length of the painful stimulation may be critical for the measurement of placebo effects, as most studies used short heat or electric shock as pain stimuli and recorded activity decreases during periods extending after the stimulus offset. This may include a later cognitive reappraisal of the significance of pain and/or late neural activity influenced by report bias.

To determine whether the expectation of analgesia exerts its psychophysical effect through changes in the perceptual sensitivity of early cortical processes (in the primary and secondary somatosensory areas) or on later cortical elaborations, such as stimulus identification and response selection in the anterior cingulate cortex, Lorenz et al.[68] used high temporal resolution techniques (magnetoencephalography). They found that activity in the secondary somatosensory cortex was highly correlated with the extent of influence of the subjective pain rating by pre-stimulus expectation. In contrast, anterior cingulate cortex activity seemed to be associated only with stimulus intensity and related attentional engagement. In another study on laser evoked potentials by Wager et al.,[69] early nociceptive components were found to be affected by placebos. Therefore a late cognitive reappraisal of the significance of pain and/or late neural activity influenced by report bias may not be responsible for this early modulation. This indicates that the early sensory components are affected by placebo manipulation.

Overall, all these brain imaging data were summarized using a meta-analysis approach with the activation likelihood estimation method.[70] Nine fMRI studies and two positron emission tomography studies were selected for the analysis. During the expectation phase of analgesia, areas of activation were found in the left anterior cingulate, right precentral, and lateral prefrontal cortex, and the left periaqueductal gray. In the phase following pain stimulation, activation was found in the anterior cingulate and medial and lateral prefrontal cortices, in the left inferior parietal lobule and postcentral gyrus, anterior insula, thalamus, hypothalamus, periaqueductal gray, and pons. Conversely, deactivations were found in the left mid- and posterior cingulate cortex, superior temporal and precentral gyri, left anterior and right posterior insula, claustrum putamen, and right thalamus and caudate body. These meta-analytic data summarize all brain imaging studies and provide a global figure of the sequence of events following placebo administration. After the activation of a pain modulatory network during the expectation and early pain phases, several deactivations occur in different areas involved in pain processing. Further clarification to the functional neuroanatomy of placebo analgesia and the meta-analysis performed by Amanzio et al.[70] comes from a more recent meta-analysis aimed at assessing whether the neurologic pain signature, which represent the set of brain regions involved in pain processing, is specifically affected by placebos.[71] In this analysis, Medline (PubMed) was searched from inception to May 2015 and involved studies of functional neuroimaging of the human brain with evoked pain delivered under stimulus intensity-matched placebo and control conditions. Data were obtained from 20 of the 28 identified eligible studies, resulting in a total sample size of 603 healthy individuals. The responses to painful stimulation compared with baseline conditions were positive in 575 participants (95.4%). Placebo treatment resulted in significant behavioral outcomes on pain ratings in 17 of 20 studies

(85%). However, placebo effects on the neurologic pain signature response were significant in only 3 of 20 studies (15%) and were very small. Similarly, analyses restricted to studies with low risk of bias indicated very small effects, and analyses of placebo responders indicated small effects. These findings indicate that placebo treatment has moderate analgesic effects on pain reports. The very small effects on neurologic pain signature are probably attributable to the fact that placebos affect pain via brain mechanisms largely independent of effects on bottom-up nociceptive processing. Placebos may act in regions other than the neurologic pain signature.

Brain connectivity has also been claimed to play a role in placebo analgesia, although this approach requires further clarification. For example, Tetreault et al.[72] found that clinical placebo response is predictable from resting-state functional magnetic resonance imaging brain connectivity in patients with chronic knee osteoarthritis pain. However, whether brain imaging can predict who will respond to a placebo and who will not remain an open question.[72]

The Reward Dopaminergic System (Fig. 17.1)

In a brain imaging study in which both positron emission tomography and fMRI imaging were used, Scott et al.[63] tested the correlation between responsiveness to placebo and a monetary reward, using a model of experimental pain in healthy subjects. They found that placebo responsiveness was related to the activation of dopamine in the nucleus accumbens, a region involved in reward mechanisms,[73] as assessed using *in vivo* receptor binding positron emission tomography with raclopride, a D2/D3 dopamine receptor agonist. The same subjects were then tested using fMRI imaging for monetary responses in the nucleus accumbens. These investigators found a correlation between the placebo responses and the monetary responses—the larger the nucleus accumbens responses to monetary reward, the stronger the nucleus accumbens responses to placebos. This study strongly suggests that placebo responsiveness depends on the functioning and efficiency of the reward system. This explains why some individuals respond to placebos, while others do not. Those who have a more efficient dopaminergic reward system would also be good placebo responders. Interestingly, Scott et al.[63] used an experimental approach that is typical of clinical trials, whereby the subjects know they have a 50% chance of receiving either placebo or active treatment and whereby no prior conditioning was performed. Thus more powerful placebo responses should have been expected if the subject knew they had a 100% chance of receiving active treatment but actually received the placebo (deceptive administration) or if prior pharmacologic conditioning had been carried out.

In a different study by the same group, Scott et al.[64] studied the endogenous opioid and dopaminergic systems in different brain regions, including those involved in reward and motivational behavior. The participants underwent a pain challenge in the absence and presence of a placebo with the expected analgesic properties. Positron emission tomography with 11C-labeled raclopride was used to analyze dopamine and 11C-carfentanil for analyzing opioids. Placebo induced the activation of opioid neurotransmission in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter. Dopaminergic activation was observed in the ventral basal ganglia, including the nucleus accumbens. Both dopaminergic and opioid activity were associated with both anticipation and perceived effectiveness of the placebo, as shown by the reduction in pain ratings. Large placebo responses were associated with greater dopamine and opioid activity in the NAc. Interestingly, nocebo responses were associated with the deactivation of dopamine and opioid release. The release of dopamine in the NAc accounted for 25% of the variance in the placebo analgesic effects. Therefore placebo and nocebo effects seem to be associated with opposite responses of dopamine and endogenous opioids in a distributed network of regions that form part of the reward and motivation circuit.

No Prefrontal Functions, No Placebo Effects

A common finding across different neuroimaging studies is the involvement of the prefrontal areas in the placebo response, such as the dorsolateral prefrontal cortex. Interestingly, Eippert et al.[54] found that the opioid antagonist naloxone blocks placebo analgesia, along with a reduction in the activation of the dorsolateral prefrontal cortex, confirming that a prefrontal opioidergic mechanism is crucial in the placebo analgesic response.

In Alzheimer's disease, the frontal lobes are severely affected, with marked neuronal degeneration in the dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex,[74] and the prefrontal lobes are responsible for complex mental functions. It is reasonable to expect a disruption of placebo responsiveness in these patients. Based on these considerations, Benedetti et al.[75] studied Alzheimer patients at the initial stage of the disease and after one year to see whether the placebo component of the therapy was affected by the disease. The placebo component of the analgesic therapy was found to be correlated with both cognitive status and functional connectivity among different brain regions; according to the rule, "the more impaired the prefrontal connectivity, the smaller the placebo response." In a more recent study, Stein et al.[76] used diffusion tensor magnetic resonance imaging to test the hypothesis of the role of white matter integrity in placebo responsiveness. The individual placebo analgesic effect was found to be correlated with white matter integrity indexed by fractional anisotropy, particularly in the right dorsolateral prefrontal cortex, left rostral anterior cingulate cortex, and periaqueductal gray. Probabilistic tractography seeded in these regions showed that stronger placebo analgesic responses were associated with increased mean fractional anisotropy values within the white matter tracts connecting the periaqueductal gray with the rostral anterior cingulate cortex and the dorsolateral prefrontal cortex.

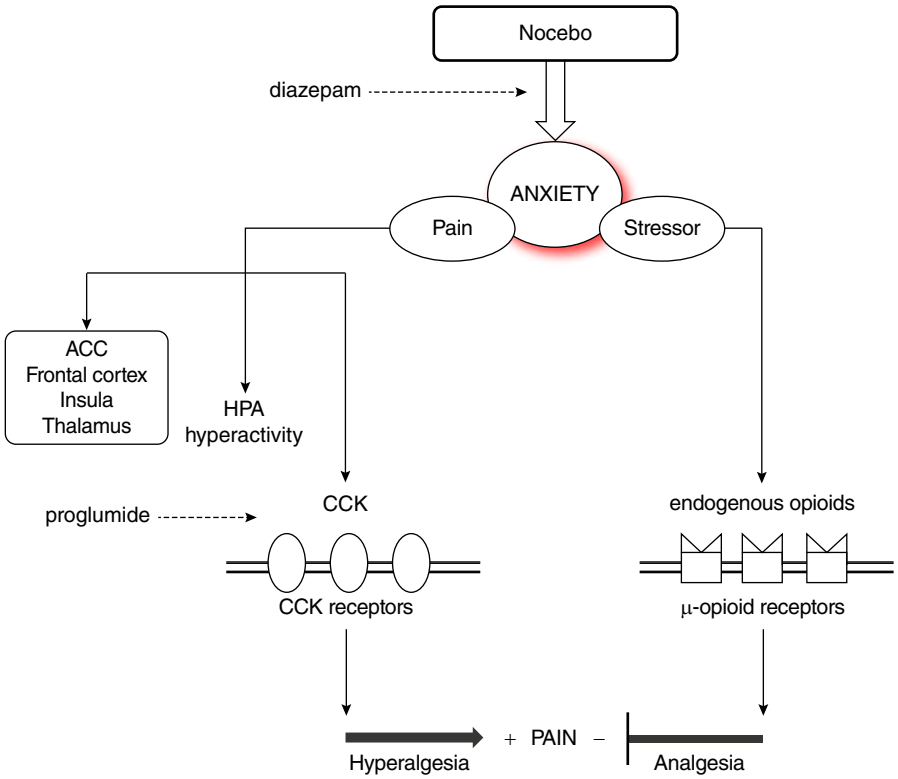
To support the crucial role of the prefrontal cortex in the occurrence of placebo responses, Krummenacher et al.[77] used repetitive transcranial magnetic stimulation (rTMS) to inactivate the prefrontal cortex during placebo analgesia. These investigators inactivated the left and right dorsolateral prefrontal cortex during a procedure inducing placebo analgesia and found that rTMS completely blocked the analgesic placebo response. Therefore inactivation of the prefrontal lobes has the same effects as those observed in prefrontal degeneration in Alzheimer disease and reduced integrity of the prefrontal white matter.

These findings have two clinical implications. First, to compensate for the disruption of placebo/expectation-related mechanisms, we need to consider a possible revision of some therapies in Alzheimer patients. Second, we should consider the potential disruption of placebo mechanisms in all conditions where the prefrontal regions are involved, as occurs in vascular and frontotemporal dementia and any lesion of the prefrontal cortex.

Nocebo Hyperalgesia (Fig. 17.2)

The nocebo hyperalgesic effects go in the opposite direction to the placebo analgesic effect because of expectations of negative outcomes. Although not always studied under strictly controlled conditions, many interesting nocebo effects and/or nocebo-like effects are present in daily life and routine clinical practice.[78,79] For example, negative diagnoses and prognoses can lead to an amplification of pain intensity and, more generally, negative communication within the healing context may have important effects on patients' emotions.[80,81] Likewise, nocebo and/or nocebo-related effects may occur when distrust toward medical personnel and therapies are present. In the latter case, unwanted effects and side effects may occur because of negative expectations,[82,83] which may reduce or even conceal the efficacy of some treatments. For example, it has been found that verbal suggestions can change the direction of nitrous oxide action from analgesia to hyperalgesia.[84] Another example is the health reports commonly issued in Western societies; negative warnings sent out by the mass media may have an important impact on the perceived symptoms of many people. Diseases with an important psychological component such as IBS are also affected by nocebo effects; sedatives and opioids in postoperative pain management have been found to be influenced by supposed nocebo effects.[85,86] Similarly, some negative expectation-inducing procedures, such as voodoo magic, may lead to symptom worsening. Finally, the fear-avoidance model of pain can be seen as a sort of nocebo-like effect, whereby the fear of pain may lead to pain worsening.[87]

The clinical trial setting is also important for nocebo effects. For example, in analgesic clinical trials, adverse events (AEs) are reported for painkillers under evaluation and compared with AEs in the placebo group. Patients who receive placebo often report a high frequency of AEs. Amanzio et al.[88] compared the rates of AEs reported in the placebo arms of clinical trials for three classes of anti-migraine drugs: NSAIDs, triptans, and anti-convulsants. It was found that the rate of AEs in the placebo arms of trials with anti-migraine drugs was high. In addition, the AEs in the placebo arms corresponded to those of the anti-migraine medication against which the placebo was compared. For example, anorexia and memory difficulties, which are typical AEs of anti-convulsants, were present only in the placebo arm of these trials. These results suggest that the adverse events in placebo arms of clinical trials of anti-migraine medications depend on the AEs of the active medication against which the placebo is compared. These findings are consistent with the expectation theory of placebo and nocebo effects. Similar findings were obtained by Mitsikostas et al. [89] for headache, Mitsikostas et al.[90] for fibromyalgia, Häuser et al.[91] for diabetic peripheral neuropathy, and Papadopoulos



• **Figure 17.2** Nocebo procedures induce anticipatory anxiety, which can be about the pain itself or about a stressor that shifts the attention from the pain. In the first case, nocebo-induced anxiety affects both the hypothalamic-pituitary-adrenal (HPA) axis and pain mechanisms; it also activates different brain regions involved in pain processing, such as the anterior cingulate cortex (ACC), frontal cortex, insula, and thalamus. Diazepam can block anxiety, thus preventing both HPA hyperactivity and hyperalgesia. CCK antagonists, such as proglumide, only block the CCK-ergic anxiety-pain link. When the general state of arousal stems from a stressful situation in the environment, an analgesic effect is observed, which derives from the activation of the endogenous opioid systems.

and Mitsikostas[92] for neuropathic pain. These authors emphasized how dropouts because of nocebo effects may confound the interpretation of many clinical trials.

In both experimental and clinical settings, it has long been known that the perceived intensity of a painful stimulus following a negative expectation of pain increase is higher than in the absence of negative expectations. For example, the expectation of painful stimulation amplifies the perceived unpleasantness of innocuous thermal stimulation,[93] and the level of expected pain intensity alters perceived pain intensity. In fact, by using two visual cues, each conditioned to one of two noxious thermal stimuli (high and low), Keltner et al.[94] showed that participants reported higher pain when the noxious stimulus was preceded by the high-intensity visual cue. Using a real nocebo procedure, whereby an inert substance was administered along with verbal suggestions of hyperalgesia, Benedetti et al.[95,96] showed expectation-induced hyperalgesia in clinical and experimental settings. In the clinical setting, the situation was a postsurgical manipulation that induced expectations of pain increase so that the patients were given an inert treatment that they expected to be painful.[95] A straightforward increase in pain was found, and this also occurred in the experimental setting using the tourniquet technique, whereby ischemic pain was induced in one arm.[96] These effects can be quite powerful, and sometimes pain can be generated from a nonpainful stimulus. For example, a study by Colloca et al.[97] used a nocebo procedure, in which verbal suggestions of painful stimulation were given to healthy volunteers before the administration of either tactile or low-intensity painful electrical stimuli. This study showed that these anxiogenic verbal suggestions could turn tactile stimuli into pain and low-intensity painful stimuli into high-intensity pain. Therefore by defining hyperalgesia as an increase in pain sensitivity and allodynia as the perception of pain in response to innocuous stimulation, nocebo suggestions of a negative outcome can produce hyperalgesic and allodynic effects. Several studies have shown that negative expectations have a significant effect on pain perception. Indeed, many recent studies have shown that nocebo effects occur in various painful conditions, ranging from experimental to clinical pain.[98,99]

Heightened anticipatory anxiety in the form of elevated autonomic arousal is important in nocebo hyperalgesia. Colagiuri and Quinn[100] found that nocebo hyperalgesia persists longer than placebo analgesia, and this difference can be explained by elevated autonomic arousal. Healthy volunteers were randomized to receive placebo conditioning, nocebo conditioning, or no conditioning using an experimental pain model with surreptitious decreases (placebo group) and increases (nocebo group) in pain stimulation paired with sham treatment during training. The pain was then assessed in the test phase with and without sham treatment at equal pain stimulation. The conditioning procedure successfully induced placebo analgesia and nocebo hyperalgesia in the relevant groups, with nocebo hyperalgesia outlasting placebo analgesia, highlighting nocebo hyperalgesia's resistance to extinction. Autonomic arousal mediated the effect of nocebo versus placebo training on extinction.

The nocebo effects can be learned through observation. Swider and Bąbel[101] and Vögtle et al.[102] studied simultaneously, but independently, voluntary participants observing a model who simulated more pain in association with either a red light[101] or the application of an ointment on the skin.[102] After the observation phase, the experimental subjects showed robust nocebo responses (i.e. hyperalgesic responses, following the presentation of the red light, and this was correlated to empathy scores).[101] Likewise, substantial nocebo responses were found after observing the ointment application, which was correlated to pain catastrophizing.[102] In addition, Swider and Babel[101] found a gender effect, whereby nocebo hyperalgesia was greater after a male model was observed compared to a female model, regardless of the sex of the experimental volunteers.

Negative expectations and nocebo effects can spread across individuals quickly by propagating negative information and communication, which may produce biochemical changes that negatively impact health and may modify the baseline of many physiologic parameters. In this context, high-altitude headaches have been studied as a model for the investigation of the products of cyclooxygenase (i.e. prostaglandins and thromboxane).[103] In this experimental model, a participant (the trigger) received negative information about the risk of headache at high altitude and disseminated this negative information across several other participants. In one week, this negative information was propagated across the 36 participants. The nocebo group showed a significant increase in headache, salivary prostaglandins, and thromboxane at high altitudes compared to the control group. In this novel experimental model, negative information propagated across 36 participants in one week.[103] Over more extended periods, hundreds or even thousands of individuals might get "socially infected," thus emphasizing the possible important role of negative social communication in the dissemination of symptoms and illness across the population. It is worth noting that interindividual communication may play a crucial role in the outcome of a clinical trial. The same authors[103] ran two "aspirin versus placebo" clinical trials at high altitudes for the control of high altitude headaches. The first trial was performed in control participants, whereas the second trial was performed in socially infected individuals. Aspirin was effective in reducing both pain and prostaglandin synthesis in the control group, whereas placebo was ineffective. Conversely, both aspirin and placebo reduced pain and prostaglandin levels in socially infected individuals. Whereas no placebo effect was present in the controls, a placebo effect occurred in the socially infected participants, a difference that is attributable to the different baseline levels of prostaglandins induced by the spread of negative information. The placebo effect occurred only in socially infected individuals because the placebo acted only on the nocebo component of the prostaglandins, and pain increased. As becomes clear from these findings, the social propagation of expectations may influence the baseline of biochemical and behavioral parameters before patients are randomized to either placebo or active treatment, thereby potentially affecting the outcome of a study. Future clinical trials should therefore consider this aspect.[104]

Nocebo-Induced Activation of Cholecystokinin (Fig. 17.2)

Compared with placebo analgesia, much less is known about nocebo hyperalgesia, mainly because of ethical limitations. Although the induction of placebo responses is acceptable in many circumstances,[105] the induction of nocebo responses is a stressful and anxiogenic procedure. To induce nocebo hyperalgesia, an inert treatment is provided along with verbal suggestions for pain increase. In 1997, a trial in postoperative patients was run with the non-specific cholecystokinin CCK-A/CCK-B (or CCK 1 and 2) receptor antagonist proglumide.[95] The situation was

a postsurgical manipulation that induced expectations of pain worsening. It was found that proglumide prevented nocebo hyperalgesia in a dose-dependent manner, even though it is not specifically a painkiller, suggesting that the nocebo hyperalgesic effect is mediated by CCK. A dose as low as 0.05 mg was completely ineffective, while a dose of 0.5 mg and 5 mg proved to be effective. As CCK is also involved in anxiety mechanisms, it was hypothesized that proglumide affects anticipatory anxiety.[95,106] Importantly, this effect was not antagonized by naloxone. However, because of ethical constraints, these effects have not been investigated further in these patients. To better understand the mechanisms underlying nocebo hyperalgesia and overcome the ethical constraints inherent to the clinical approach, a similar procedure was used in healthy volunteers in whom experimental pain was induced.[96] It was found that the oral administration of an inert substance and verbal suggestions of hyperalgesia induced both hyperalgesia and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis as assessed using adrenocorticotropic hormone (ACTH) and cortisol plasma concentrations. Both nocebo-induced hyperalgesia and HPA hyperactivity were blocked by benzodiazepine diazepam, suggesting the involvement of anxiety mechanisms. In contrast, the administration of the mixed CCK-A(1)/CCK-B(2) receptor antagonist, proglumide, blocked nocebo hyperalgesia completely but did not affect HPA hyperactivity, suggesting a specific involvement of CCK in the hyperalgesic but not in the anxiety component of the nocebo effect. Interestingly, neither diazepam nor proglumide showed analgesic effects on baseline pain, as they acted on the nocebo-induced pain increase only. These data suggest that a close relationship between anxiety and nocebo hyperalgesia exists but that proglumide does not act by blocking anticipatory anxiety, as previously hypothesized.[95,106] Instead, it interrupts a CCK-ergic link between anxiety and pain. Therefore in contrast to the anxiolytic action of diazepam, proglumide blocks a CCK-ergic pronociceptive system that is activated by anxiety and is responsible for anxiety-induced hyperalgesia. Nocebo hyperalgesia is an interesting model to better understand when and how endogenous pronociceptive systems are activated. The pronociceptive and anti-opioid action of CCK has been documented in many brain regions.[78,107,108] CCK has been shown to reverse opioid analgesia by acting at the level of the rostral ventromedial medulla,[109,110] and activates pain-facilitating neurons within the rostral ventromedial medulla.[111]

The discrepancy between anxiety-induced hyperalgesia and stress-induced analgesia may only be apparent. Stress is known to induce analgesia in a variety of situations, both in animals and humans. When one is under stress, the pain threshold increases. However, the nature of the stressor is likely to play a central role. Although hyperalgesia may occur when the anticipatory anxiety is about the pain itself,[93,94,96,112] analgesia may occur when anxiety is about a stressor that shifts the attention from the pain.[113] We should therefore use these two definitions in two different ways.[79] In the case of anxiety-induced hyperalgesia, we are talking about the anticipation of pain, in which attention is focused on the impending pain. We have seen that the biochemical link between anticipatory anxiety and pain increase is represented by the CCK-ergic systems. Conversely, stress-induced analgesia should be considered whenever a general state of arousal stems from a stressful situation in the environment, so that attention is now focused on environmental stressors. There is experimental evidence that analgesia results from the activation of endogenous opioid systems.[113]

Neuroimaging of Negative Expectations and Nocebo Hyperalgesia (Fig. 17.2)

Modern brain imaging techniques are fundamental to our understanding of the neurobiology of negative expectations. No inert substance is generally provided in these studies, and the experimenter typically uses verbal suggestions. Therefore in this case, it is better to discuss the nocebo-related effects. Typically, the experimenter told the participant about the forthcoming pain to make the subject expect a painful stimulation, and both the anticipatory and post-stimulus phases were analyzed. Using this experimental approach, Sawamoto et al.[93] found that the expectation of painful stimulation amplifies the perceived unpleasantness of innocuous thermal stimulation. These psychophysical findings were correlated with enhanced transient brain responses to non-painful thermal stimuli in the anterior cingulate cortex, parietal operculum, and posterior insula. This enhancement consisted of both a higher intensity signal change (in the anterior cingulate cortex) and a larger volume of activated voxels (in the parietal operculum and posterior insula). Therefore expecting a painful stimulus enhances both the subjective unpleasant experience of an innocuous stimulus and the objective responses in some brain regions.

Overall, negative expectations may result in the amplification of pain,[114,115] and several brain regions, such as the anterior cingulate cortex, prefrontal cortex, and insula, have been found to be activated during the anticipation of pain.[68,94,112] These effects are opposite to those elicited by positive expectations, whereby expectations of reduced pain are investigated. In fact, in some studies in which both positive and negative outcomes have been studied using the same experimental approach, modulation of subjective experience and brain activation has been found. For example, in a study by Koyama et al.,[112] as the magnitude of expected pain increased, activation increased in the thalamus, insula, prefrontal cortex, and anterior cingulate cortex. In contrast, expectations of decreased pain reduced activation of pain-related brain regions, such as the primary somatosensory cortex, insular cortex, and anterior cingulate cortex. In a different magneto-electroencephalographic study in which source localization analysis was performed, Lorenz et al.[68] found modulation of the dipole in the secondary somatosensory cortex by nocebo-like and placebo-like suggestions. The dipole was modulated in the same direction as expectations, shrinking when a decrease in pain was expected and expanding when an increase in pain was anticipated. In another study, Keltner et al.[94] found that the level of expected pain intensity alters the perceived pain intensity, along with the activation of different brain regions. By using two visual cues, each conditioned to one of two noxious thermal stimuli (high and low), these investigators showed that subjects reported higher pain when the noxious stimulus was preceded by the high-intensity visual cue. By comparing the brain activation produced by the two visual cues, they found significant differences in the ipsilateral caudal anterior cingulate cortex, head of the caudate, cerebellum, and contralateral nucleus cuneiformis. Interestingly, the imaging results of this study indicate that expectation and noxious stimulus intensity act in an additive manner on afferent pathways activated by cutaneous noxious thermal stimulation.

Somehow, unlike previous studies, Kong et al.[116] investigated nocebo responses by administering an inert treatment that the participants believed to be hyperalgesic. These investigators showed that, after administering the inert treatment along with

negative suggestions, subjective pain intensity ratings increased significantly more in nocebo regions than in the control regions in which no expectation manipulation was performed. fMRI analysis of hyperalgesic nocebo responses to identical calibrated noxious stimuli showed signal increases in brain regions, including the bilateral dorsal anterior cingulate cortex, insula, superior temporal gyrus, left frontal and parietal operculum, medial frontal gyrus, orbital prefrontal cortex, superior parietal lobule, and hippocampus; right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus. Functional connectivity analysis of spontaneous resting-state showed a correlation between two seed regions (left frontal operculum and hippocampus) and pain network, including the bilateral insula, operculum, anterior cingulate cortex, and left primary somatosensory and motor cortices. Therefore nocebo hyperalgesia may be predominantly produced through an affective-cognitive pain pathway (medial pain system), and the left hippocampus may play an important role in this process.

The early enhancement of pain signals in the dorsal horn of the spinal cord has also been found in a study in which nocebo hyperalgesia was investigated in combination with spinal fMRI in healthy volunteers.[117] The local application of an inert nocebo cream on the forearm increased pain ratings compared with a control cream and reduced pain thresholds on the nocebo-treated skin. Pain stimulation induced a strong activation in the spinal cord at the level of the stimulated dermatomes C5/C6, and comparison of the nocebo with the control condition revealed enhanced nocebo-related activity in the ipsilateral dorsal horn of the spinal cord. Therefore the nocebo hyperalgesic effect envisages a pain-facilitating mechanism at a very early stage of pain processing, particularly in the spinal cord, well before cortical processing. The effects of nocebo on the spinal cord have also been found for complex psychological factors, such as information about a drug, for example, the price tag. Tinnermann et al.[118] discovered that labeling an inert treatment as an expensive medication led to stronger nocebo hyperalgesia than labeling it as an inexpensive medication. This effect was mediated by activity in the prefrontal cortex and coupling between the prefrontal areas, brainstem, and spinal cord. This might represent a mechanism through which higher cognitive representations, such as values, can modulate early pain processing.

Nocebo effects have also been found to be associated with a decrease in dopamine and opioid activity in the nucleus accumbens, thus underscoring the role of the reward and motivational circuits in nocebo effects.[64]

Communication Strategies

Overall, these findings may have implications both in clinical trial settings and in medical practice. Communication strategies that reduce the development of nocebo side effects while maintaining informed consent are of considerable interest. For example, framing how information about the likelihood or significance of side effects is presented (e.g. negative frame: 30% will experience headache vs. positive frame: 70% will not experience headache) may reduce nocebo effects.[119] In addition, a study was specifically aimed at testing whether positive mood induction can block the development of nocebo effects.[120] Healthy participants were assigned to one of four conditions. First, participants took part in a mood induction procedure, with half receiving a positive mood induction and the other half a neutral mood induction. Then, participants were told they would experience transcranial direct current stimulation (tDCS); half of them were informed that headache pain is a side effect of tDCS, whereas the other half were not given this information. Positive mood was induced using a video (a portion of the movie "City Slickers 2"), whereas the neutral video contained a portion of a history of golf documentary. Both video compilations had a total viewing time of approximately 15 min. In the neutral mood condition, the provision of headache side effect information led to a greater occurrence of headaches, more frequent headaches, and a higher maximum level of headache pain compared to those with no side effect information. In the positive mood condition, a similar increase in headache pain did not manifest from the provision of side effect information. Therefore, a positive mood induction can block the formation of nocebo effects that arise from side effect information.

Conclusions

The neuroscientific approach to placebo research and the consequent new knowledge on the neurobiological underpinnings is to pay dividends and bodes well for the future. At least three important implications can be envisaged: First, the neuroscience of placebo and nocebo effects helps us understand several complex brain functions, such as the top-down modulation of pain. Second, new experimental designs can be devised that can help better interpret clinical trials, such as the measurement of patients' expectations. Third, the doctor-patient relationship can be improved by adopting communication strategies that affect the endogenous mechanisms of pain modulation.

Key Points

- Most knowledge about the neurobiologic mechanisms of the placebo effect comes from the field of pain and analgesia.
- The expectation of pain reduction plays a crucial role in placebo analgesia. This is shown by the reduced effectiveness of painkillers when administered covertly (unexpectedly).
- The placebo analgesic effect is mediated by endogenous opioid systems and antagonized by cholecystokinin in some circumstances. In other conditions, the endocannabinoid system is involved.
- Many brain imaging studies indicate that several areas are involved in placebo analgesia, including the dorsolateral prefrontal cortex and the regions involved in dopaminergic reward mechanisms.
- The prefrontal lobes are fundamental to a placebo response. If there was no prefrontal control, there was no placebo response.
- The nocebo hyperalgesic effect is mediated by anxiety, which activates a cholecystokinin system that facilitates pain transmission.
- Endogenous pain modulatory descending circuits represent a biological substrate for the action of placebos on pain.
- This new knowledge about the mechanisms of placebo and nocebo effects has important implications for both clinical trials and medical practice.

Suggested Readings

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PART 3

Clinical Evaluation and Assessment

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18

History and Physical Examination of the Patient With Pain

CHARLES E. ARGOFF, GRACE FORDE, SAYED E. WAHEZI, ROBERT DUARTE

This chapter provides an overview of appropriate history taking and a structured approach to the physical examination of a pain patient, along with the anatomic and physiologic basis of the physical findings. Physical examination serves to further explore and confirm the findings from the clinical history. Data obtained from the history are essential to pair with the physical exam to create a thoughtful differential diagnosis of the etiology of the pain so that the need for further diagnostic testing can be determined and further assist in treatment planning.

The history is one of the most important pillars of proper pain assessment. The importance of this aspect of clinical evaluation cannot be overemphasized. Many practitioners adopt the "PQRST" approach to historical evaluation. Using such, a patient is asked what provokes or palliates their symptoms (P), the nature of its quality (Q), whether/where it radiates (R), the severity of their pain (S), and temporal components (T). Assessing the person in pain also requires additional careful consideration of pain physiology, anatomy, functional limitations, and the patient's ability to convey the information. The practitioner needs to understand the onset of symptoms (insidious or traumatic), types of daily activities limited by pain, psychological effects of pain, and the presence of neuroanatomic vs. referral or co-incidental pain radiation. This information is required to discern whether the patient's pain is nociceptive, neuropathic, nociplastic, or other types of pain. It is important to understand that many people experiencing chronic pain are not exclusively experiencing one type or the other, but rather may have varying degrees of each, thus mixed pain types. Complete and personalized history taking is essential to understanding a patient's pain and properly devise a treatment strategy to improve life quality. The time and effort spent completing this are likely to be of value when treating a person in pain.

The key components of the physical examination include a general physical examination, a detailed neurologic examination, a detailed musculoskeletal examination, and an examination for cutaneous or trophic findings. The musculoskeletal examination includes inspection, palpation, percussion, auscultation, and provocative maneuvers.[1]

General Physical Examination

Vital signs, including temperature, heart rate, respiratory rate, blood pressure, and weight, should be noted at each visit. This information is useful in forming an impression of the overall health and comorbid conditions of the patient.

A few moments should be spent observing and documenting the general appearance and gait of the patient. Whenever possible, the examining physician should make every effort to bring the patient back to the examining room from the waiting room. This allows the physician the opportunity for examination as the patient transitions from sitting to standing and ambulates to the examining room. This observation time allows an "unofficial" examination that may reveal inconsistencies not noted on the "official formal" examination.

Observations include how the patient dresses and personal hygiene. Pain behavior, posture, and anatomic abnormalities such as contractures, amputation, and asymmetries should also be noted. Maladaptive postural dynamics play an important role in generating myofascial pain. Excessive lumbar lordosis places strain on the lumbar extensor muscles and results in low back pain. Similarly, forward flexion of the cervical spine with drooping of the shoulders strains the cervical paraspinous and scapular muscles and thereby causes neck and upper back pain.

Evaluation of gait includes assessment of stride length, base, arm swing, and stability. An unsteady, wide-based ataxic gait can be seen in patients with cerebellar and proprioceptive disorders. In patients with hip and lower extremity pain, the stance phase is reduced in the affected limb, along with a shortened swing phase on the uninvolved side, which results in an antalgic gait pattern. A waddling gait can occur in patients with weakness of the hip girdle muscles or bilateral degenerative hip joint disease. Many gait deviations can occur in patients with foot drop, including vaulting, steppage gate, circumduction, and persistent abduction of the affected limb.[2]

Neurologic Examination

Components of the neurologic examination include:

- mental status examination
- cranial nerve testing
- motor strength examination
- deep tendon reflexes
- sensation
- coordination
- special tests

Mental Status Examination

A reasonable assessment of mental status can often be made as part of history taking and inquiry into activities of daily living and function. A basic mental status examination includes assessment

of the level of consciousness; orientation to person, place, time, and situation; registration and short-term memory; attention and concentration; and assessment of language for aphasia. The Folstein Mini-Mental Status Examination is a useful screening tool for detecting cognitive deficits and dementia.

Assessment of mood, affect, suicidal and homicidal ideation, and neurovegetative symptoms such as sleep, appetite, and energy level should be assessed routinely. This helps uncover comorbid psychiatric conditions (e.g. depression, anxiety, and psychosis), which can have a profound impact on the treatment of pain patients.

Cranial Nerve Testing

The cranial nerve examination localizes pathology primarily at the level of the brainstem. Central pain conditions associated with brainstem pathology (e.g. strokes, tumors, demyelinating disease, and vascular malformations) can be associated with cranial nerve deficits.[2]

Cranial Nerve I

Olfactory Nerve

Test one nostril at a time. Odors such as coffee, mint, or cloves can be used. Noxious odors such as ammonia are avoided because they activate trigeminal nerve receptors in the nasal passages.

The most common cause of smell dysfunction is nasal and sinus pathology. Dementia, neurodegenerative conditions, and basal frontal tumors can also result in smell dysfunction.

Cranial Nerve II

Optic Nerve

Visual acuity is determined with a Snellen chart. Visual fields are tested by the confrontation method at the bedside. More formal visual field testing with perimetry can be requested if indicated. Pupillary reaction to light and accommodation tests the optic and ophthalmic nerves. Funduscopic examination is done to evaluate the optic disc and retina. Papilledema and enlargement of the blind spot can occur in conditions associated with elevated intracranial pressure, including idiopathic intracranial hypertension, which is a relatively common cause of intractable headache.

Cranial Nerves III, IV, and VI

Ophthalmic, Trochlear, and Abducens Nerves

These nerves control eye movement and can be tested by asking the patient to track a moving object in the eight positions of cardinal gaze. Eyelid elevation and pupillary constriction are controlled by the third cranial nerve and are evaluated by assessing the direct, consensual, and accommodation reflexes. Sympathetic fibers innervate the pupillary dilator muscles. Horner's syndrome exists in several clinical conditions, including after stellate ganglion blockade. This syndrome includes ipsilateral ptosis, miosis, and anhidrosis. However, the mechanism of these changes involves sympatholysis and is independent of cranial nerve function.

Cranial Nerve V

Trigeminal Nerve

This nerve supplies sensory input to the face, mouth, tongue, and scalp up to the vertex. The mandibular division of the trigeminal nerve also supplies the muscles of mastication (i.e. temporalis, masseter, medial, and lateral pterygoid muscles).

Sensation along the ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve are tested with temperature, pinprick, and light touch. The trigeminal nerve also provides the afferent limb of the corneal blink reflex.

Peripheral lesions of the trigeminal nerve result in ipsilateral loss of facial sensation with weakness and atrophy of the ipsilateral jaw muscles.

Cranial Nerve VII

Facial Nerve

The facial nerve innervates the muscles of facial expression, the submandibular and lacrimal glands, and taste in the anterior two-thirds of the tongue. Testing is usually limited to checking facial motor function (e.g. forehead wrinkling, eye closure, smile, pursing lips, and corneal blink). Supranuclear lesions of the seventh nerve typically spare the forehead, whereas nuclear and infranuclear lesions do not.

Sensory testing of the facial nerve is not routinely performed but can be accomplished by applying sweet, sour, and salt stimuli to the ipsilateral half of the anterior two-thirds of the tongue.

Cranial Nerve VIII

Vestibulocochlear Nerve

The vestibulocochlear nerve mediates hearing and balance. Hearing can be assessed with a 512 Hz tuning fork. The Rinne and Weber tests are commonly used to assess for sensorineural and conductive deafness.

In the Weber test, the base of a gently vibrating tuning fork is placed on the midforehead or the vertex. The patient is asked which ear hears the sound better. Normally, the sound is heard equally in both ears. With unilateral sensorineural hearing loss, the sound is better in the unaffected ear. With unilateral conductive hearing loss, sound is perceived better in the affected ear.

The Rinne test is conducted by placing the base of a gently vibrating tuning fork on the mastoid bone behind the ear. When the patient can no longer hear the sound, the fork is quickly moved next to the patient's ear. In patients with sensorineural deafness and normal hearing, air conduction is better than bone conduction. With conductive deafness, bone conduction is better than air conduction.

Nystagmus noted on eye movement testing may be a sign of vestibular dysfunction. In patients with complaints of episodic vertigo, the Dix-Hallpike maneuver is useful for making the diagnosis of benign paroxysmal positional vertigo. The test is performed by rapidly moving the patient from a sitting to a supine position while the patient's head is turned 45° to the right. The patient should remain supine with head turned for 20-30 s and then returned to the sitting position. The observation of rotatory nystagmus with limited duration is what is considered clearly positive. The response is noted, and then the test is repeated as described above with the head now turned to the left.[3]

Examination of the vestibulocochlear nerve can be informally done by observing the patient when conversing to determine grossly if they are having difficulty hearing speech. To formally test the vestibulocochlear nerve, the examiner should create a soft sound, usually through a whisper or finger rubbing, next to each ear. This should be done with each ear individually and the opposite ear covered. The patient should be asked if the sound was equal on both sides, and a normal finding would be that there was no difficulty hearing the noise in either ear or that it was equal in both ears. If the patient notices decreased sound on either ear, the ear canals should be inspected with an otoscope to ensure that the tympanic membrane is intact and that there is no material such as wax or exudate physically blocking the canal that would interfere with the patient's hearing.

Cranial Nerve IX

Glossopharyngeal Nerve

The glossopharyngeal nerve subserves taste in the posterior third of the tongue and sensation in the pharynx. It provides the afferent limb of the gag reflex.

Cranial Nerve X

Vagus Nerve

The vagus nerve innervates the pharyngeal and laryngeal muscles and forms the efferent limb of the gag reflex. Symptoms of vagus nerve lesions include dysarthria and dysphagia.

Cranial Nerve XI

Accessory Nerve

The cranial segment of the accessory nerve supplies the muscles of the larynx, whereas the spinal segment innervates the trapezius and sternocleidomastoid muscles. These muscles are tested by an ipsilateral shoulder shrug and contralateral head turn maneuvers.

Cranial Nerve XII

Hypoglossal Nerve

The hypoglossal nerve provides motor supply to the tongue. Testing is performed by tongue protrusion and pushing the tongue against the cheek on either side. Lesions of the hypoglossal nerve produce ipsilateral deviation on tongue protrusion.

Motor Strength Examination

Before muscle testing, the examiner should observe for any involuntary movements, for example, resting tremor, which could suggest extrapyramidal dysfunction or fasciculations observed in peripheral nerve disorders. Next, tone should be assessed by passively moving the patient's upper or lower extremity while in a seated position, determining normal, increase, or decrease in tone. An increase in tone can be divided into spasticity, which is velocity dependent seen in upper motor neuron disease involving the brain or spinal cord, and rigidity, defined as an increase in tone persisting throughout the entire range of motion. Decrease in tone is typically seen in peripheral nerve pathology

Manual muscle testing is performed by asking the patient to place each muscle in its position of maximal mechanical advantage. Muscle strength is commonly assessed with the Medical Research Council scale (Table 18.1).[3] Grades one to three are relatively objective and less prone to interobserver variation. Grade one implies a palpable contraction but with no associated movement noted. Grade two implies an ability to move the limb with gravity eliminated (this may require special positioning to assess). A grade three finding on motor examination is consistent with the ability to move against gravity but an inability to move against further resistance. The gastrocnemius muscle presents unique challenges when performing a manual muscle test. In the case of the gastrocnemius, a grade three muscle is able to perform one toe raise with the patient standing and lightly holding onto something for balance. A grade four muscle is able to perform five toe raises, and a grade five gastrocnemius is capable of performing ten toe raises. Grades four and five are difficult to standardize among different examiners. Factors such as a patient's body habitus, age, and expected functional status, and examiner strength, contribute to the difficulty of grading muscle strength above grade three.[3]

The screening muscle strength examination should correspond to a template that evaluates sequential nerve roots and peripheral nerves. Tables 18.2 and 18.3 summarize the commonly tested muscles along with their corresponding nerve root and peripheral nerve innervation.[4]

The muscle strength examination depends significantly on patients' comprehension and effort. Suboptimal or volitional lack

TABLE 18.1 Medical Research Council Grading of Muscle Strength

Grade 0	No movement
Grade 1	Flicker of movement
Grade 2	Movement only with gravity eliminated
Grade 3	Full range of movement against gravity
Grade 4	Full range of movement against some resistance
Grade 5	Full power against resistance

TABLE 18.2 Upper Extremity Muscles: Innervation and Action

Muscle	Action	Nerve Root	Nerve
Infraspinatus	Shoulder external rotation	C5-6	Suprascapular
Deltoid	Shoulder abduction, extension, and flexion	C5-6	Axillary
Biceps	Forearm flexion and supination	C5-6	Musculocutaneous
Triceps	Forearm extension	C7-8	Radial
Brachioradialis	Forearm flexion in the midprone position	C6	Radial
Extensor carpi radialis longus and brevis	Wrist extension	C6-7	Radial
Flexor carpi ulnaris	Wrist flexion with ulnar deviation	C8-T1	Ulnar
Flexor digitorum profundus	Flexion at the distal interphalangeal joints	C7-8	Anterior interosseus branch of the median nerve
Abductor pollicis brevis	Abduction of the thumb	C8	Median
Adductor pollicis longus	Abduction of the thumb	C8-T1	Ulnar

TABLE 18.3 Lower Extremity Muscles: Innervation and Action

Muscle	Action	Nerve Root	Nerve
Iliopsoas	Hip flexion	L2-4	Femoral
Adductor longus and brevis	Hip adduction	L2-4	Obturator
Gluteus maximus	Hip extension	L5-S2	Inferior gluteal
Gluteus medius and minimus	Hip abduction	L5-S2	Superior gluteal
Quadriceps femoris	Knee extension	L2-4	Femoral
Hamstrings (i.e. semitendinosus, semimembranosus, and biceps femoris)	Knee flexion	L5-S1	Sciatic
Tibialis anterior	Foot dorsiflexion	L4-5	Deep peroneal
Extensor hallucis longus	Extension of the big toe	L5	Deep peroneal
Peroneus longus	Foot eversion	L5	Superficial peroneal
Gastrocnemius/soleus	Foot plantar flexion	S1-2	Tibial
Tibialis posterior	Foot inversion and plantar flexion	L5-S1	Tibial

of effort may be apparent as "give-way weakness," with the patient applying intermittent resistance to the examiner interspersed with moments of nearly complete cessation of effort. Weakness resulting from radiculopathy, focal compressive peripheral neuropathy, diffuse peripheral neuropathy, or myopathy fit specific patterns. A nonphysiologic pattern should raise suspicion for potential psychogenic weakness. The Hoover test is useful to detect psychogenic weakness of the lower extremities. The patient is examined while lying supine in bed and is asked to elevate the paretic leg. The examiner's hand should be placed underneath the contralateral heel. A positive Hoover test result occurs if the patient fails to exert a downward force on the examiner's hand. The Hoover sign is based on the crossed extensor reflex mediated by interneurons in the spinal cord. This reflex was first described by Sherrington and can be demonstrated in decorticate animals.[2]

Reflex Testing

The deep tendon reflexes are mediated by a monosynaptic arc. The afferent limb is provided by sensory fibers, which innervate muscle spindles. These fibers project centrally toward the spinal cord and synapse with alpha motor neurons in the ventral horn. The alpha motor neurons comprise the efferent limb of the reflex arc. It is important to note that normal individuals can have diminished deep tendon reflexes. The Jendrassik maneuver can be used to elicit deep tendon reflexes in this situation. The patient is asked to interlock the fingers of both hands and pull them apart. Jaw clenching can also be used to achieve a similar effect. Lesions of the afferent or efferent limb of this arc can cause diminished or absent deep tendon reflexes. This includes conditions such as peripheral neuropathy and radiculopathy. However, patients with small-fiber neuropathy have preserved deep tendon reflexes because the neural deficit spares large myelinated Ia fibers.

TABLE 18.4 Grading of Deep Tendon Reflexes

Grade 0	Absent
Grade 1+	Hypoactive
Grade 2+	Normal
Grade 3+	Spread of reflex contraction to muscles innervated by the adjacent root level
Grade 4+	Sustained clonus

TABLE 18.5 Nerve Root Innervation of the Deep Tendon Reflexes

Muscle Tendon	Nerve Root Level
Biceps	C5-6
Brachioradialis	C6
Triceps	C7-8
Quadriceps femoris	L3-4
Gastrocnemius/Achilles tendon	S1-2

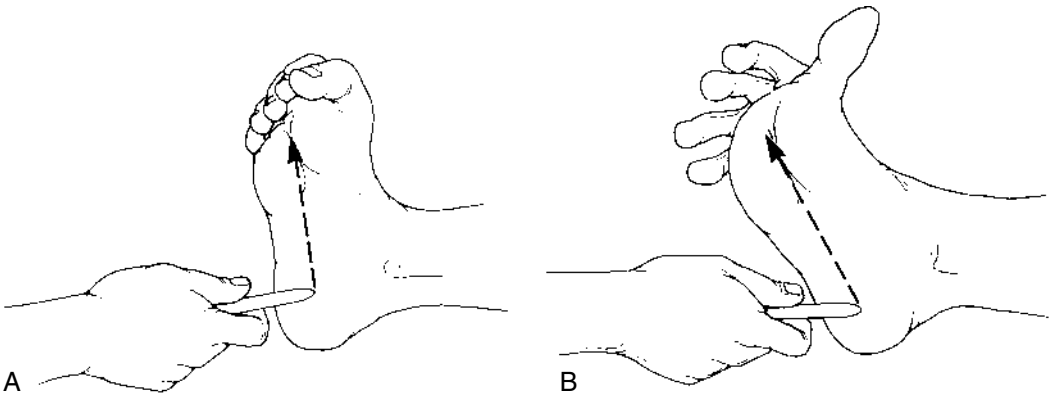
Deep tendon reflexes are best examined with a Queen Square or Troemner hammer while the patient is seated comfortably in the upright position. Table 18.4 explains the grading of deep tendon reflexes. Table 18.5 reviews the important deep tendon reflexes and their corresponding nerve root level.

Upper motor neuron lesions cause hyperreflexia. The Babinski and Hoffman signs may be present in patients with upper motor neuron dysfunction. A subtly positive Hoffman response can be seen in young women and people taking selective serotonin reuptake inhibitor anti-depressants, and in these scenarios may not represent pathology. The Babinski sign is elicited by stroking the lateral aspect of the sole of the foot with a blunt object (e.g. a disposable wooden spatula). A positive sign is indicated by the extension of the great toe (Fig. 18.1). Care should be taken to not stimulate the more medial aspect of the sole, which will evoke a withdrawal response. Hoffman's sign is elicited by briskly flicking the dorsal or volar aspect of the distal phalanx of the middle finger. Reflex flexion of the index finger and thumb constitutes a positive response.[5]

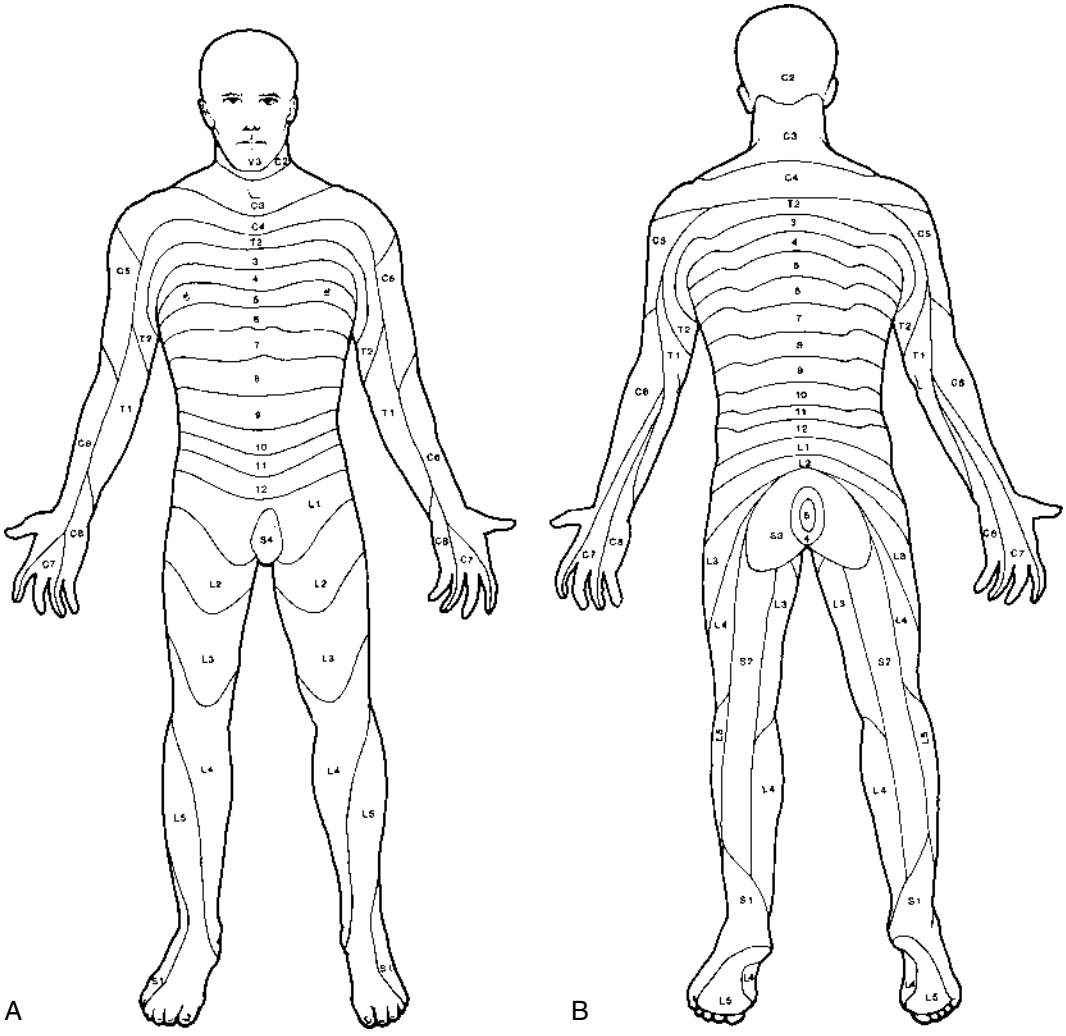
Sensation

A sensory examination should include the modalities of temperature, pinprick, proprioception, and vibration. Pinprick and temperature are mediated by Aδ and C small fibers and are transmitted in the spinal cord by the lateral spinothalamic tract. Proprioception and vibration are mediated by Aβ large fibers and are carried by the dorsal columns in the spinal cord.

Pinprick testing can be performed with a clean disposable safety pin. A distal-to-proximal pattern of testing is useful in evaluating patients with length-dependent peripheral neuropathy. In patients with nerve root pathology, testing in a dermatomal



• **Figure 18.1** Babinski test. **A**, Normal. **B**, Abnormal.



• **Figure** 18.2 Anterior (**A**) and posterior (**B**) dermatomes of the body. (From Baker AB, Baker LH. *Clinical neurology*. Vol 1. New York: Harper & Row, 1983.)

pattern is recommended (Fig. 18.2). Temperature sensation can be assessed rapidly using the cold metal portion of a tuning fork and warm water in a test tube. The format for testing is identical to that for pinprick testing.

Patients with neuropathic pain (pain as a consequence of a lesion of the somatosensory system) may demonstrate several key findings during the neurologic examination, including allodynia, hyperalgesia, hypoalgesia, wind up, and hyperpathia. Allodynia is defined as experiencing pain when a stimulus that normally does not generate pain is applied. To test for allodynia, a stimulus that normally does not generate pain, such as light touch, is applied, and if present, the patient will experience pain. Hyperalgesia is defined by increased sensitivity and response to painful stimuli beyond what is expected normally. Testing for hyperalgesia should

be done through sensory testing methods that generate mild amounts of pain using a sharp object such as a clean disposable safety pin. While a mildly painful reaction to these stimuli is normal, a patient with hyperalgesia will indicate increased pain in the affected area.

Hypoalgesia is decreased sensitivity and response to painful stimuli. Wind up is the increase in pain intensity over time when a given stimulus is delivered repeatedly above a critical rate.

Hyperpathia is characterized by an exaggerated and often delayed pain response to stimuli.

Proprioception is assessed at individual synovial joints. The most sensitive test for proprioception involves the interphalangeal joint of the big toe. The toe is grasped at its lateral margins between the thumb and index finger of the examiner's hand. The big toe is then abducted from the remaining toes and moved superiorly and inferiorly in increments of 5 degrees while the patient's eyes are closed. The patient is then asked to identify whether the toe is being moved up or down. If proprioception is impaired at the toe, the same test can be repeated at the ankle, knee, and distal interphalangeal joint of the index finger.

Vibration sense is usually examined by placing a vibrating 128 Hz tuning fork over a distal bony prominence. The dorsal surface of the interphalangeal joint of the big toe, medial malleolus, tibial tuberosity, and patella are the relevant lower extremity landmarks. The distal phalanx of the index finger, distal end of the radius, and olecranon process of the ulna are the important sites for testing vibration in the upper extremity. Recently, the Rydel-Seiffer 64 Hz quantitative tuning fork has been shown to have a better correlation than the traditional 128 Hz tuning fork with sural nerve sensory nerve action potential and ankle reflex results.[6]

Coordination

The cerebellar function can be divided into midline/vermal and hemispheric functions. The vermis controls axial coordination and balance, whereas the hemispheres coordinate the limbs. Vermal function is assessed by observation of gait and standing balance. The hemispheric function is assessed with the finger-to-nose and heel-to-shin tests. Other tests include rapidly alternating movements (e.g. sequential hand pronation and supination) and examination for motor tone, which is reduced in patients with cerebellar disease. Chronic alcohol abuse and long-term use of medications such as phenytoin can cause acquired cerebellar degeneration.[5,7,8,9]

Musculoskeletal Examination

The musculoskeletal examination serves to evaluate the integrated functioning of bones, joints, supporting ligaments, muscle, and tendon. Information from the examination can be used to assess complicating sources of pain in various structures, including the skin, subcutaneous tissue, peripheral nerves in entrapment zones, and viscera. The format of the musculoskeletal examination follows the steps of inspection, palpation, range of motion, and special tests. The components tested are the spine (cervical, thoracic, lumbar), upper and lower trunk girdles, and their respective extremities and joints.

Spinal Examination

Inspection of the cervical and thoracolumbar spine provides information on posture and alignment. Abnormal kyphosis, lordosis, or scoliosis should be noted when the patient is not aware of being formally examined (i.e. when the patient is sitting or standing upon providing history). Reduction of the scoliosis angles may be observed when the patient flexes the spine, which may also change the treatment. Percussion of the spinous processes can reveal localized tenderness, which is seen in patients with conditions such as vertebral compression fractures, epidural tumors, or abscesses. The spinous process should have a similar inter-spinous process distance in the patient who does not have appreciable kyphosis or lordosis; an increase in inter-spinous process distance across 1-2 may be indicative of a vertebral compression fracture with appreciable height loss (>50%). Tenderness in the paraspinous regions can be seen in patients with facet arthropathy and myofascial pain syndrome. Special tests, such as facet loading, may distinguish the two, but it is not uncommon for patients to have both pathologies. The normal range of motion of the cervical spine is 60 degrees of forward flexion, 75 degrees of extension, 45 degrees of lateral flexion, and 80 degrees of lateral rotation. Range of motion testing should be performed with the patient in both the supine and sitting positions. Improvement in range of motion in the supine position suggests that posterior muscle spasm is responsible for restricting cervical mobility. Anterior cervical spasms/range of motion may worsen when a patient is placed supine. However, there is no positional improvement in cervical range of motion with cervical arthropathy.

A positive abduction tension release sign is highly specific in determining whether the shoulder pain is secondary to C5-6 root compression or shoulder pathology. The test is performed by asking the patient to abduct the affected arm such that the forearm is placed in a resting position on top of the patient's head. With shoulder pathology, attempts to achieve this position will cause pain. In patients with C5-6 root compression, this test position will commonly result in a marked reduction in pain in the shoulder and medial scapular (rhomboid) region. The Spurling maneuver is highly specific for confirming the diagnosis of cervical radiculopathy. The patient is asked to perform simultaneous lateral flexion and extension of the neck toward the symptomatic side. Provocation of the ipsilateral neck and arm pain constitutes a positive Spurling sign.[10,11]

The normal thoracolumbar spine range of motion is 90 degrees of forward flexion, 30 degrees of back extension, 25 degrees of lateral flexion, and 60 degrees of lateral rotation. Pain provoked by simultaneous lumbar extension and lateral rotation is suggestive of ipsilateral facet arthropathy because these maneuvers result in zygapophyseal joint loading. Pain provoked by forward flexion may suggest with a discogenic or vertebral body source of pain because flexion causes axial loading. However, lumbar flexion can also induce pain of the pathologic sacroiliac ligaments and facet capsules. Therefore the practitioner must use ROM in the context of other examinations for a more targeted diagnosis. Lumbar discogenic pain symptomatology is controversial but commonly agreed to be restricted to the axial spine and can be associated with intolerance of the sitting position and pain provoked by coughing, sneezing, and Valsalva maneuvers.

Myofascial Examination

Myofascial pain is manifested by the presence of tender palpable bands of muscle called trigger points. Active myofascial trigger points are associated with complaints of spontaneous pain and restricted range of motion. Latent trigger points are tender and palpable on direct examination, but they do not produce spontaneous pain.

A myofascial examination should start with an assessment of posture and joint function to determine any underlying cause of the regional myofascial pain. Myofascial trigger points can be identified by gentle palpation in the direction of muscle fibers. Trigger points can be felt as a ropelike region of nodularity. Trigger points also are exquisitely tender, and palpation produces local and referred pain. The referral pain pattern may mimic a radicular or peripheral nerve distribution. Commonly affected muscles include the trapezius, gluteus, and cervical and lumbar paraspinous musculature, but many others may be affected as well. Tender points are painful to palpation but do not radiate.[12]

Examination of the Extremities

Inspection and, when indicated, measurement of the extremities may reveal discrepancies in limb length, deformities, and alterations in muscle bulk. Multiple upper extremity joint range of motion can be demonstrated by asking the patient to perform specific tasks such as raising the hands above the head. Gross shoulder, elbow, wrist, and finger movement can be assessed using this compound maneuver. If the patient can place both palms on the back of the head and dorsum of the hand behind at the mid lumbar region without significant difficulty, it can be reasonably concluded that the patient can perform most basic daily activities of living. The lower extremities can be assessed during the evaluation of gait. The pattern of gait abnormality can direct the clinician to the underlying cause of dysfunction, such as foot drop, leg length discrepancy, or hip or knee pain.[10,11,13,14]

Upper Extremity

Shoulder Joint Examination

The inspection should evaluate the symmetry, bulk of the deltoid muscles, and posture. Palpation of the shoulder joint should include the sternoclavicular joint, clavicle, acromioclavicular joint, glenohumeral joint, and the scapular spine and scapulothoracic articulation. The normal range of motion for the shoulder joint is 180 degrees of flexion and extension in the sagittal plane, 180 degrees of abduction and adduction in the frontal plane, 90 degrees of external rotation, and 40 degrees of internal rotation. Common chronic causes of shoulder pain include glenohumeral arthritis, acromioclavicular arthritis, subacromial or subdeltoid bursitis, rotator cuff, and bicipital tendonitis, calcific tendonitis, and adhesive capsulitis. Traumatic acute and subacute shoulder pain may be because of dislocations, labral lesions, commonly noted as superior labrum anterior to posterior lesions. Various special tests are used to diagnose these conditions. The tests most commonly used in clinical practice are described below.

Pain on shoulder abduction (arm 90 degrees from torso) and internal rotation are seen with impingement syndrome. The etiology involves the entrapment of supraspinatus between the humeral head and the coracoacromial arch. Subacromial bursitis, and supraspinatus strains, can result as a consequence of chronic impingement syndrome. In case of a complete supraspinatus tear, the patient will be unable to hold the arm in an abducted position after passive abduction to 90 degrees. Horizontal abduction in the plane of the scapula (45 degrees from the torso) with the thumb turned down—the empty can test—is a sensitive test for rotator cuff pathology. It is important to note that all examinations with shoulder abduction should be done with the practitioner placing their hand on the top of the shoulder to prevent scapular rotation, which can artificially increase the degree of abduction. Untreated tears of the rotator cuff tendons result in disuse atrophy of the scapular muscles, and a dip seen in the supraspinatus fossa can suggest a chronic tear. The drop arm test is used to diagnose complete rotator cuff tears. The patient's arm is passively abducted to 90 degrees and then released. Failure to maintain shoulder abduction suggests a complete rotator cuff tear. The diagnosis can be investigated further with magnetic resonance imaging. Complete tears in atraumatic settings are often because of chronic supraspinatus tendonitis.

Adhesive Capsulitis

Frozen shoulder, or adhesive capsulitis, is characterized by a diminished range of motion at the scapulothoracic and glenohumeral joints. There is progressive fibrosis of the shoulder joint capsule, which disrupts normal shoulder mobility and scapulothoracic rhythm. Normally, the shoulder joint can be abducted to 180 degrees. Scapulothoracic motion begins at 90 degrees of shoulder abduction, and there is a 2:1 ratio of glenohumeral to scapulothoracic motion. Adhesive capsulitis results in gradual loss of range of motion, with little to no shoulder movement present in advanced cases. Adhesive capsulitis is diagnosed when extension and abduction in the affected shoulder is less than 50% of the non-affected shoulder.

Elbow Joint

Inspection of the elbow joint includes assessment of humeral and radial-ulnar symmetry. The carrying angle between the arm and forearm is measured with the patient standing and the arms at the side and facing anteriorly. The normal carrying angle is 10 to 15 degrees of valgus for men and up to 18 degrees for women. Readily palpable landmarks of the elbow joint include the olecranon process and the medial and lateral epicondyles. Normal range of motion at the elbow starting from the anatomic position is 0 degrees of extension to 150 degrees of flexion at the humeroulnar joint and 170 degrees of pronation and supination at the radioulnar joint.

Lateral Epicondylitis

Overuse of the forearm extensor muscles results in inflammation of the common extensor tendon insertion at the lateral epicondyle. Patients report constant elbow pain that is worse with resisted or weighted wrist extension. Pain over the lateral epicondyle confirms the diagnosis of lateral epicondylitis. In severe cases, a passive extension of the wrist or mild palpation of the lateral epicondyle may also replicate pain in the extensor mass.

Medial Epicondylitis

This condition is similar to lateral epicondylitis and results from overuse of the forearm flexor muscles. Pain is experienced over the medial epicondyle and can be reproduced by resisted or weighted resisted wrist flexion. Severe cases can be reproduced with mild palpation of the medial epicondyle.

Wrist Joint

Inspection plus palpation of the wrist joint is used to evaluate joint symmetry. The range of motion is 60 degrees of extension, 70 degrees of flexion, 20 degrees of abduction, and 30 degrees of adduction. The most common clinically encountered specific wrist joint pain disorder is carpal tunnel syndrome. This entity results from entrapment of the median nerve at the wrist, which causes numbness of the #1-3 digits. In more severe cases, symptoms present with pain. Thumb

weakness results from very significant median nerve entrapment; thumb abduction is the most compromised movement because of abductor pollicis brevis wasting. A diagnosis of carpal tunnel syndrome is supported by the presence of the Tinel and Phalen signs. In the Tinel sign, percussion of the proximal volar wrist crease produces paresthesia in the thumb and index and middle fingers of the symptomatic hand. To elicit the Phalen sign, the patient is asked to flex both wrists and place the dorsum of each hand against one another for 1 min, mechanically compromising the carpal tunnel space. An already irritated nerve will respond by causing painful numbness when affected this way. Reproduction of sensory dysesthesias in a median nerve distribution is consistent with a positive Phalen test. Caution must be used when interpreting the results of these tests because neither test has a high degree of specificity or sensitivity. The "gold standard" test for the evaluation of suspected carpal tunnel syndrome is formal electrodiagnostic testing.

Evaluation of the Digits

The digits are inspected to evaluate for symmetry and the presence of any deformities. Heberden's nodes at the distal interphalangeal joints and Bouchard's nodes at the proximal interphalangeal joints can be seen in patients with osteoarthritis. Range of motion can be assessed by asking patients to open and close their fist. The normal range of motion in the sagittal plane is 90 degrees at the metacarpophalangeal joints, 120 degrees at the proximal interphalangeal joints, and 70 degrees at the distal interphalangeal joints. The first metacarpophalangeal joint has 50 degrees of motion in abduction, 50 degrees in adduction, and 35 degrees in opposition. Metacarpal phalangeal swelling with or without ulnar deviation of digits may suggest rheumatoid arthritis; this finding can direct diagnosis and treatment strategies with patients who have neck, hip, or knee pain, as these symptoms are commonly associated with the condition.

Evaluation of the Hip Joint

Inspection of the hip joint should pay attention to symmetry, muscle bulk, and surgical scars. The normal range of motion at the hip is 100 degrees of flexion, 30 degrees of extension, 20 degrees of adduction, and 40 degrees of abduction. With the hip joint in a flexed position, the range of motion is 45 degrees for internal rotation and 40 degrees for external rotation. Hip pain may result from the pathology of the acetabulum, femoral neck or head, periosteum, or joint capsule. It may also result from abnormalities in a surrounding structure such as the bursae or may be referred from the lumbar spine or sacroiliac joint. Hip joint pathology classically presents as groin pain and anteromedial thigh pain, especially when crossing the affected thigh over the non-affected thigh in a seated position. Upper lateral thigh pain over the greater trochanter region, when palpated, can be because of greater trochanteric bursitis or gluteus medius tendinopathy. Practitioners must consider that hip pain complaints because of knee pathology can also cause anteromedial thigh pain. Additionally, lateral thigh pain can be seen as a "typically atypical" referral pain pattern of L5 radiculopathy, with pain involving the L5-innervated gluteal muscles.

As one can see, pain referral patterns alone are often insufficient to diagnose the etiology of hip pain, and an appropriate imaging evaluation is helpful in this regard.

Trochanteric Bursitis

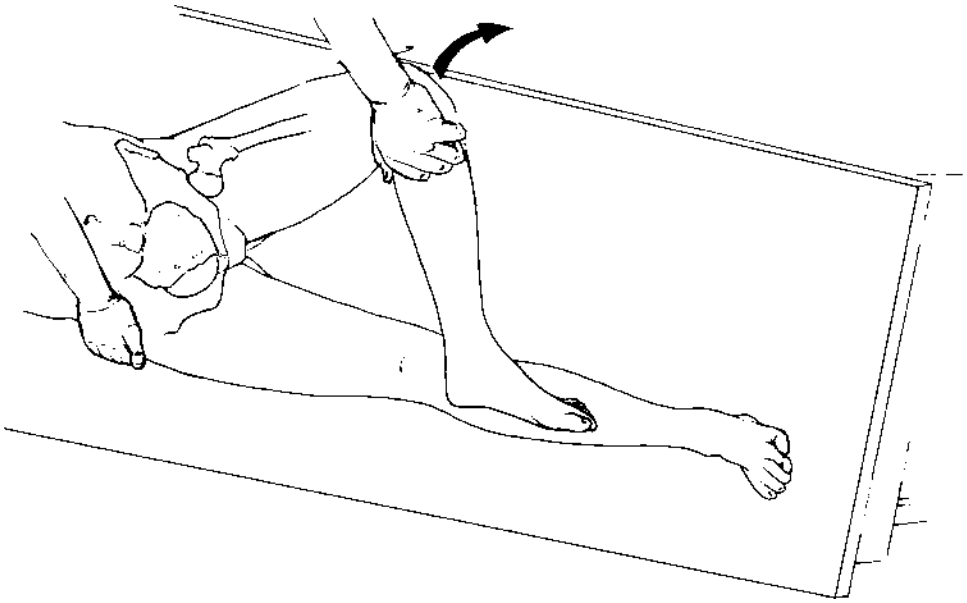
Patients report a deep, dull, aching pain with radiation to the lateral hip region. The pain is worse when the patient lies on the affected side. Serious cases can cause difficulty with walking and sit to stand transfers. Inflammation primarily involves the trochanteric bursa, which lies between the gluteus maximus and gluteus medius tendons. The diagnosis is supported by the tenderness with palpation over the greater trochanter and pain on hip extension and resisted hip abduction.

Patrick's Test

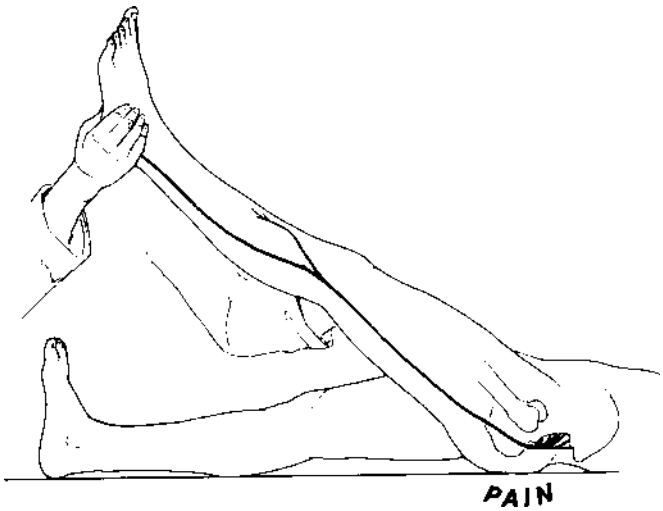
Patrick's test evaluates hip and sacroiliac joint pathology. With the patient in the supine position, the examiner passively flexes, abducts, and externally rotates the hip. Pain in the groin suggests hip joint pathology, whereas sacroiliac pain indicates dysfunction of the sacroiliac joint (Fig. 18.3).

Straight-Leg Raise Test

The examiner passively elevates one leg with the patient in the supine position by holding it at the ankle. The hip is flexed to an angle of 70 to 90 degrees, with the knee extended (Fig. 18.4).



• **Figure 18.3** The Patrick or flexion abduction external (FABER) test.



• **Figure 18.4** Straight-leg raise test (Lasègue's sign).

A positive straight-leg raise test produces pain starting at the hip with radiation down to the ankle. Pain that remains localized to the posterior thigh region is caused by tension on the hamstrings. A crossed straight-leg raise sign is present if testing of the uninvolved leg produces contralateral symptoms. Both the straight and crossed straight-leg raise tests place the lumbosacral nerve roots under tension, and a positive test is suggestive of lumbosacral radiculopathy. Straight-leg testing can also be performed with the patient in the seated position. In this setting, the patient is asked to extend the knee. This stretches the lumbosacral roots as the hip is flexed to 90 degrees when the patient is seated. If augmentation is needed, the patient can be asked to dorsiflex the foot, or the examiner can passively dorsiflex the patient's foot if needed.

Evaluation of the Knee

Inspection should assess symmetry, the position of the patella, surgical scars, and the bulk of the surrounding musculature, including the quadriceps femoris muscle. The patient should be visualized when they are performing stand to sit and sit to stand transfer, as an extended knee may suggest knee pathology. Particular attention should be placed on inspection of the vastus medialis because this muscle atrophies rapidly when patients have chronic knee pain and reflex inhibition of quadriceps function. Varus deformity (knees bowed outward, away from the midline) of the knee results from medial compartment loss, whereas valgus deformity (knees bowed inward, toward the midline) is caused by lateral compartment loss. Palpation should include the surrounding bursae (i.e. the pes anserinus and prepatellar bursae) because these are common sources of pain. The normal range of motion at the knee joint is 150 degrees in the sagittal plane.

Special Tests

Drawer Sign

With the patient's knee in the flexed position and the foot anchored to stabilize the lower part of the leg, the examiner draws the tibia anteriorly. Movement of the tibia in the forward direction constitutes a positive anterior drawer sign and suggests a tear of the anterior cruciate ligament. Similarly, if the tibia moves posteriorly when pulled backward, this is a positive posterior drawer sign and is caused by a torn posterior cruciate ligament (Fig. 18.5).

Patellar Femoral Grinding Test

Knee pain on rising to a standing position or while climbing stairs can occur with chondromalacia patellae. With the patient's knee extended, the examiner exerts downward pressure on the patella into the femoral groove. Patients with chondromalacia patellae will complain of pain with this maneuver.

Apley's Compression or Grinding Test

This test is used to evaluate for medial and lateral meniscal tears. With the patient in the prone position, the knee is flexed to 90 degrees, a downward force is applied to the heel, and the tibia is rotated medially and laterally against the femur (Fig. 18.6). Pain provoked in the medial or lateral aspect of the knee indicates a tear in the respective collateral ligament.

Evaluation of the Ankle

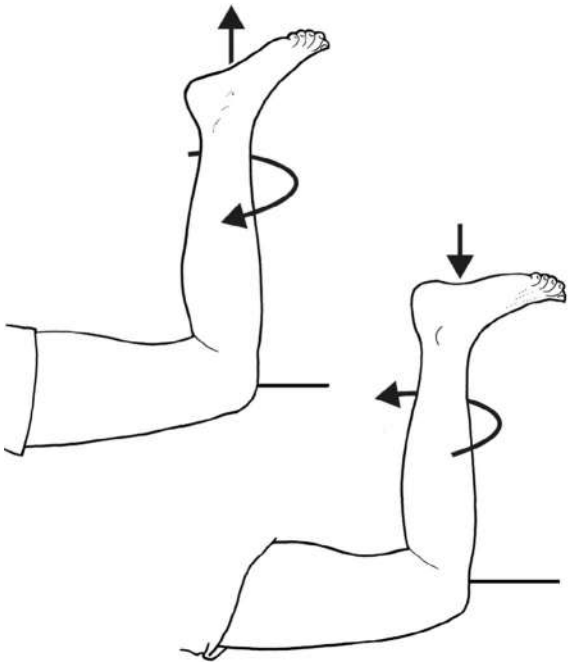
Inspection should include evaluation of bony landmarks, symmetry, and edema. The normal range of motion of the ankle is 20 degrees of dorsiflexion and 40 degrees of plantar flexion through the tibiotalar joint. The 30 degrees of inversion and 15 degrees of eversion noted at the ankle result from subtalar motion, not tibiotalar motion.

Pain and excessive motion on pulling the ankle joint anteriorly indicate a tear in the anterior talofibular ligament, whereas similar findings on forced inversion occur with tears of the calcaneofibular ligament. The posterior talofibular ligament is usually damaged only in patients with a significant history of preceding trauma.

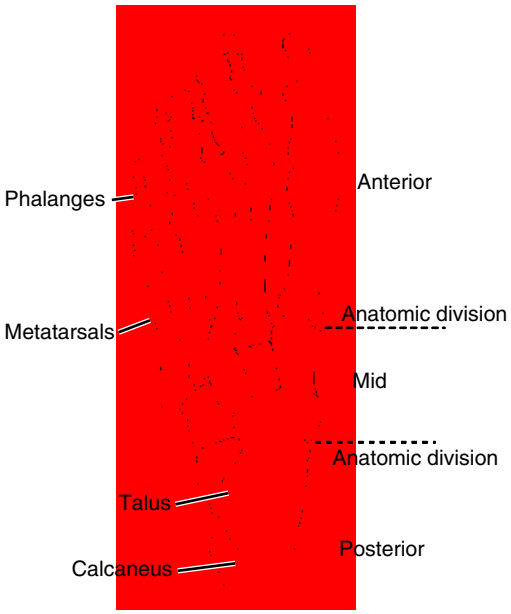
Evaluation of the Foot

Functional assessment of the foot is targeted toward its anterior, middle, and posterior segments. The anterior segment consists of the five metatarsal and 14 phalangeal bones; the middle segment includes the navicular, cuboid, and three cuneiform bones; and the posterior segment includes the talus and calcaneus (Fig. 18.7).

• **Figure 18.5** Drawer sign test for the cruciate ligaments. The standard drawer sign test for the cruciate ligaments immobilizes the foot and stresses the lower part of the leg on the femur. Pulling the leg forward tests the anterior cruciate ligament, whereas posterior pressure tests the posterior cruciate ligament. (Redrawn from Calliet R. *Knee pain* and *disability*. 3rd ed. Philadelphia: FA Davis; 1992, pp. 1–69.)



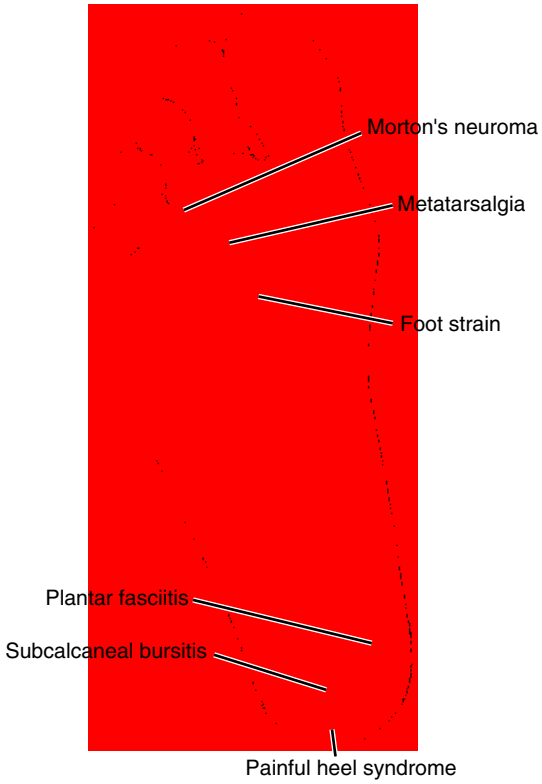
• **Figure 18.6** Examination of ligament injury, including the meniscus (Apley's test). The Apley test checks the integrity of the knee ligamentous structures and the menisci. It is performed in two aspects. *Left*, With the patient prone and the knee flexed to a right angle, downward pressure is applied to the lower part of the leg. The leg is then rotated to test the menisci. This maneuver compresses the menisci between the femoral condyles and the tibial plateau, as in the McMurray test. With the lower part of the leg internally rotated, the medial meniscus is tested. Grating, crepitation, limitation, and pain imply meniscal damage. From the same position, the leg is elevated (*right*), which places traction on the ligaments. Excessive motion, deduced by comparison to the contralateral side, indicates laxity or injury to the knee ligaments and capsule. (Redrawn from Calliet R. *Knee pain and disability*. 3rd ed. Philadelphia: FA Davis; 1992, pp. 1–69.)



• **Figure 18.7** Anatomy of the foot with functional segmentation. (Redrawn from Abrams B, Glaser L. Painful conditions of the foot and ankle: evaluation and treatment. *Pain Diagn* 1997;7:351–363.)

The posterior segment of the foot transmits body weight to the ground. The middle segment provides flexibility and the ability to adapt gait to uneven surfaces. The anterior segment acts as a fulcrum to provide forward thrust during ambulation. The impact of the foot against the ground is cushioned by its longitudinal and transverse arches.

Foot pain is a common symptom in patients (Fig. 18.8). The more common pain syndromes that are diagnosed by physical examination are described in the following sections.



• **Figure. 18.8** Location of common painful conditions involving the plantar surface of the foot. (Redrawn from Abrams B, Glaser L. Painful conditions of the foot and ankle: evaluation and treatment. *Pain Diagn* 1997;7:351–363.)

Tarsal Tunnel Syndrome

In tarsal tunnel syndrome, the posterior tibial nerve is entrapped beneath the lancinate ligament, posterior to the medial malleolus. Patients complain of pain and paresthesia affecting the toes and sole of the foot. Physical examination may demonstrate atrophy of the intrinsic foot muscles and hypoesthesia of the sole of the foot. Percussion posterior to the medial malleolus can provoke paresthesia in the ipsilateral sole and toes in patients with tarsal tunnel syndrome.

Morton's Neuroma

Morton's neuroma is characterized by pain between the metatarsal bones, usually between the third and fourth toes and less commonly between the second and third toes. The pain is reproducible on palpation of the space between the metatarsal heads. The etiology of Morton's neuroma is not well understood, but it probably represents a form of interdigital neuritis. Interestingly, surgically resected specimens in patients with Morton's neuroma do not show any significant changes in nerve histology when compared with control tissue obtained from cadavers.[15]

Metatarsalgia

Pain in patients with metatarsalgia occurs on weight bearing and is localized to the plantar aspect of the metatarsal heads. The pain occurs maximally over the first metatarsal head and can be reproduced by direct palpation. With foot inversion, weight is shifted to the heads of the second and third metatarsal bones, and repetitive stress can result in pain over these sites. Patients may walk with a characteristic antalgic gait, with the foot being held in the inverted position. This can serve as a useful clue to the diagnosis.

Foot Strain

Foot strain affects the middle segment of the foot. Repetitive patterns of overuse result in elongation of the longitudinal arch and alterations in the normal alignment of the talus and calcaneus. Elongation of the longitudinal arch produces excessive strain on the plantar fascia, medial collateral ligament, and talocalcaneal ligament. Physical findings include flattening and pain on compression of the longitudinal arch.

Plantar Fasciitis

Plantar fasciitis is manifested as plantar foot pain on weight bearing. Patients often have a history of prolonged standing in footwear lacking arch support or on hard surfaces. Inflammation develops at the point of attachment of the plantar fascia to the calcaneus. Calcaneal bone spurs can develop from chronic straining of the plantar fascia. Clinically, tenderness on palpation can be elicited over the anterior portion of the calcaneus with radiation into the plantar fascia. A common finding is pain the first thing in the morning. Patients will frequently note severe plantar foot pain with weight bearing on arising and temporary improvement with weight bearing or after the morning shower.

Painful Heel Syndrome

Painful heel syndrome results from degenerative changes in the weight bearing aspect of the calcaneus and occurs primarily in morbidly obese individuals or those who stand or walk excessively. Pain is often worse in the morning on waking up or after prolonged rest. The examination is significant for tenderness on palpation over the posterior portion of the plantar aspect of the calcaneus.[1]

Tests for a Nonorganic Etiology of Pain

Waddell's Signs

Waddell's tests were intended to evaluate patients with low back pain for functional overlay. There are five signs in total, and the presence of any three of these five signs in a patient was considered suggestive of a nonorganic pain etiology.[16]

- Tenderness to palpation
  - Widespread skin tenderness with a light touch
  - Tenderness on deep palpation that is not restricted to a single anatomic area
- Simulation
  - Low back pain provoked by axial loading pressure on the skull of a standing patient or rotation of the shoulders and pelvis in the same plane resulting in increased low back pain
- Distraction
  - For example, a patient with a positive response to the straight-leg raise test in the supine position but no pain on the same test repeated in the sitting position
- Regional disturbance in function
  - Weakness involving multiple muscle groups in a nonmyotomal distribution with "give-way" effort
  - Sensory loss in a segmental pattern (e.g. glove-stocking rather than a dermatomal distribution) observed in a patient in whom polyneuropathy is not an appropriate diagnosis

Overreaction

Disproportionate facial or verbal behavior (e.g. moaning and grimacing on light touch, posturing, and withdrawing from the examiner)

A higher number of Waddell signs have been associated with failure of interventional treatments for low back pain.[17] However, there are several limitations of Waddell's signs. Widespread superficial tenderness is commonly found in patients with fibromyalgia, and tenderness on deep palpation is part of myofascial pain syndrome. Sensory loss in a glove-stocking distribution is present with peripheral polyneuropathy. Moreover, studies have not found a consistent relationship between the presence of Waddell's signs and subscale scores on the Minnesota Multiphasic Personality Inventory. Data suggest that Waddell's signs cannot accurately distinguish between organic and nonorganic causes of pain.[18,19]

History taking and completing an appropriately thorough physical examination is helpful in elucidating the cause of a patient's pain complaints, especially when conducted and interpreted in the context of appropriate diagnostic studies. The COVID-19 pandemic has brought about with it many challenges to health care and, with respect to the content of this chapter, conducting a history and physical examination of the person in pain. When many patient encounters are being completed through telemedicine, the initial pain consultation is currently often not completed face-face in person but through a phone and/or video link. As this trend may continue for the foreseeable future and perhaps even after the pandemic, a multi-disciplinary group of pain specialists convened and have published a guide to best practices for the multi-disciplinary approach for assessment via telemedicine of the person in pain. In addition, a different group has developed a video guide to the virtual neurologic examination. While each of the assessments described in this chapter may not be able to be completed through telemedicine, many can and must be considered when completing a telemedicine visit with a pain patient in keeping with best practices.[20,21] Whether in person or virtually, the history and physical examination of the person in pain is an essential component of that person's treatment.

Suggested Readings

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19

Electromyography and Evoked Potentials

ANDREW DUBIN

In almost all instances, tests and/or studies can help elucidate the cause of a problem. However, of equal, and possibly greater, importance is the potential for a test to introduce data that clouds the picture and adds complicating factors that can result in a delay in diagnosis or in arriving at the wrong conclusions.

In the evaluation of a patient with pain, particular caution must be taken to guard against the thought process of "if the test is abnormal, that must be the cause of the problem."

Electrodiagnostic medicine (EDX) is potentially a powerful tool that allows for the objective quantification of the function of the peripheral nervous system. However, in all instances, the data must be interpreted within the context of the patient, and ideally, the test should be tailored to address questions and concerns that arose from the detailed history and physical exam that preceded the EDX study.

The question of the utility of EDX in the evaluation of a patient with pain, and more importantly, the limitations and potential pitfalls must always be first and foremost in the mind of the EDX physician and referring physician when setting up, performing, and interpreting the data.

Understanding the role of EDX in evaluating the pain patient is critical to avoid the over and under interpretation of the data. In all instances, the successful evaluation and treatment of a patient lie in the blending of the history and physical with appropriate data utilization.

Electrodiagnosis is a broad term that includes multiple techniques. This chapter will focus on needle electrode examination (NEE) and motor and sensory nerve conduction studies (NCSs), including late responses. Needle electromyography (EMG) and standard motor and sensory nerve conduction techniques, including in limited scenarios the use of late responses, can be useful adjuncts to the physical examination of patients in pain, with the understanding that the history and objective findings on the physical exam drive the electrodiagnostic examination (EDX) investigation, as opposed to the pitfall of attempting to retrofit the EDX data to the patient.

Conditions in which EDX may be of use include painful peripheral neuropathies, entrapment neuropathies, traumatic nerve injuries, radiculopathies, lumbar spinal stenosis, arachnoiditis, and painful myopathies.

More recently, there has been an increased reliance on anatomic measures such as intradermal nerve biopsy for small fiber neuropathy and magnetic resonance imaging for larger neural structures. Unfortunately, this "anatomic" approach is a snapshot in time and cannot fully delineate if the process is acute versus chronic nor assist in delineating the relapsing/remitting nature of many chronic pain disorders. Additionally, the "anatomic" approach fails to recognize the inherently complex nature of pain, a subjective experience with a myriad of modifiers that can only be correlated with the clinical picture.

The problems inherent in applying electrodiagnostic techniques to diagnose and manage pain are no different from those encountered in history taking, physical examination, radiologic evaluation, and therapeutic diagnostic testing (e.g. nerve blocks). Pain is a subjective experience, often without an objective, gold standard test. As such, the final diagnosis of the probable cause and presumptive treatment of a pain syndrome is a clinical one that can be supported only by relevant data, including findings on EDX.

The standardization of EDX techniques and robust data on normal individuals allows for the objective electrophysiologic assessment of the peripheral nervous system to gain an overall understanding of the distribution of abnormalities, if present, or relative normalcy, if not. The distribution of abnormalities may correlate strongly with the cause of a disease process causing pain or can be an incidental finding of unclear significance. The ability to distinguish between these two scenarios rests in the correlation of EDX data to symptoms. Hence the physical exam findings and historical data should drive the EDX study. EDX testing should not be undertaken to address the question of "let us see what could be wrong?"

Questions that can be posed and potentially answered through using electrodiagnostic techniques include some of the following:

Is a disease of large myelinated nerve fibers present?

What is its pattern of distribution? Is it mononeuropathy, polyneuropathy, or mononeuritis multiplex?

Does it equally affect motor and sensory fibers, or does one dominate?

Does the distribution of abnormalities suggest involvement at the nerve root, plexus, or more distal nerve level?

If there is a disease process involving a single (or multiple) nerve, such as injury or compression, is it improving, worsening, or static? Understand that this may require serial studies over time.

Is the nerve involved motor, sensory, or mixed?

Is a disease of muscles present?

Is the process one of nerve, muscle, or both?

Are small fibers selectively involved, or is this mainly a large-fiber disorder, or are both involved? (Understand that patients with isolated small fiber neuropathy will have normal EDX findings on needle EMG and NCSs. In these instances, skin biopsy assessment for intra-epidermal nerve fiber density and sweat gland analysis may aid in the diagnosis).

Is there autonomic and somatic involvement?

Are more proximal structures rather than distal ones involved?
Is the central nervous system involved? Standard EDX testing in this scenario is utilized to rule out peripheral nervous system involvement.
Is the process acute, chronic, acute on chronic, or old?

EDX testing satisfies two fundamental steps in the assessment of a neuropathic pain syndrome before any attempt at therapy: (1) rigorously establishing the presence or absence of a peripheral nervous system lesion and (2) determining the relevance of an established peripheral neuropathic lesion or myopathic process to the subjective clinical complaint. In addition, with the advent of new treatments, including enzyme replacement and the potential insertion of genetic material into cells, early diagnosis and the ability to monitor treatment outcomes objectively become of great importance. Recent enzyme replacement therapy for Pompe's disease is an example of the potential diagnostic, therapeutic, and prognostic importance of electrodiagnosis.[1]

The parent organization of electrodiagnosis is the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), which has promulgated a Recommended Policy for Electrodiagnostic Medicine Position Statement.[2] This document seeks to lay out the scope of electrodiagnosis by using consensus expert opinion to ensure adequate examination while attempting to conserve scarce resources by listing the indications for testing and the maximum number of studies per diagnosis in 90% of cases. Since there has been some abuse of the number of studies done on patients and since many pain specialists are not familiar with the techniques of electrodiagnosis, this serves as an important source of information on the appropriate measures to be used when these diagnostic methods are being considered.

Electromyography

EDX is a method of testing both the anatomic and physiologic integrity of lower motor neuron structures (anterior horn cells, nerve roots, plexuses, peripheral nerves, neuromuscular junction, and muscles), sensory components, and some spinal and brainstem reflex pathways.[3–5] The term electromyography previously caused considerable confusion because strictly speaking, it was NEE of muscle function but often was expanded to include nerve conduction velocity (NCV) or NCSs and other tests. However, its common usage has come to mean needle EMG, determination of NCV, and less frequently, testing such as the H-reflex and F-response, cranial nerve reflexes (e.g. the blink reflex), and studies of the neuromuscular junction. The all-inclusive term EDX (electrodiagnostic examination) is used here to avoid confusion among tests.

A puzzling dichotomy regarding pain and electrodiagnostic testing in the medical literature is well documented. The reason for the paucity of references appears to be at least in part the attitudes of pain specialists themselves, who point out that "large caliber afferent fibers are physiologically unrelated to pain," a submodality mediated by small caliber fibers. Additionally, the test is unable to explore the basis for positive sensory phenomena generated by dysfunction even of large caliber afferent channels.

Electrical Testing of Nerves and Muscles

All electrodiagnostic equipment can fundamentally be thought of as containing the following componentry:

Electrodes: Electrodes allow for the recording of an evoked signal. The recording device may be surface or needle electrodes. The size (area) of the recording surface directly impacts the amplitude and duration characteristics of the recorded response. As such, the consistency of electrode size is paramount when comparing studies across time and between examiners and institutions.[3]

Stimulator: Stimulators can be constant voltage or constant amperage; typically, they are now constant current. An understanding of Ohms law (V=IR) quickly allows one to appreciate that If R (resistance) varies (skin impedance, sweat) over time, holding I (current) constant allows for the maintenance of a constant and stable electrical field (load despite variations in resistance). This results in improved tolerance for the test with less pain (stable intensity) and more stable recordings over time.[4–7]

High-gain differential amplifier: Differential amplifiers have both high frequency (low pass) and low frequency (high pass) characteristics. The frequencies that pass between the filters is the band path and is adjustable for environmental situations. Changing the amplifiers will impact on amplitude, duration, and latency of the recorded responses. It is critical to appreciate this phenomenon to avoid over or under interpretation of data accumulated in electrically challenging environments such as ICUs.[4–7]

Recording display or central processing device with A to D conversion capability: A to D conversion refers to the mathematical manipulation of the analog signal into a stable static waveform "seen" on the oscilloscope screen. The waveform "seen" is the digital representation of the analog wave resulting from multiple digitized (x, y coordinate) points.[6,7]

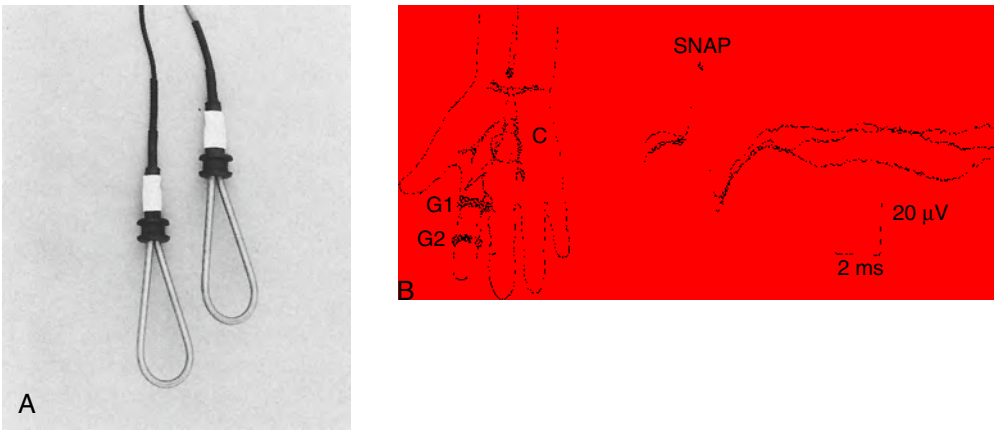
The EMG apparatus amplifies and displays biologic information derived from either surface or needle electrodes. Electrical information may be recorded from muscles, nerves, or other nervous system structures and is displayed on an oscilloscope. Besides the visual display on the oscilloscope, a permanent recording may be made, audio amplification may allow it to be heard over a loudspeaker, and analog-digital analysis of signals may be used. Nerves are electrically stimulated to measure conduction.[6,7]

For NCSs, skin surface electrodes are generally used for recording compound muscle or nerve action potentials. Rarely, needle electrodes are used.

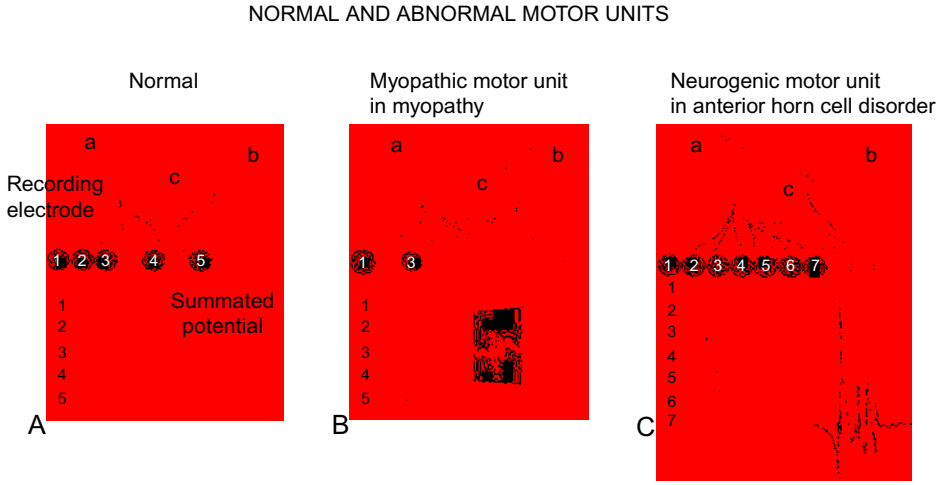
For needle EMG, needle electrodes are used. They are typically monopolar or concentric. Each has unique characteristics and does impact on amplitude, duration, and phase complexity. Understanding these factors is important when comparing studies conducted by different examiners and different labs.[3,6,7]

For sensory testing, ring electrodes, self-adhering surface electrodes, and disc electrodes are used for measurement (Fig. 19.1). Modern EMG equipment is manufactured by numerous companies and is generally standardized to allow reliable and reproducible testing by different laboratories, but normative data, including data for special populations such as geriatric, pediatric, diabetic, and even active workers, may differ among laboratories and require standardization by each laboratory.[5–7]

NEE is an invasive procedure, but complications are rare. However, patients should be apprised of them. The most common is transient muscle soreness. Aseptic precautions should be observed. Safeguards for testing include extra care with patients who are taking warfarin or other anticoagulants or who have hemophilia or other blood dyscrasias, but since most muscles tested are superficial, they can easily be compressed, and the bleeding abated. Severe thrombocytopenia is a relative contraindication and should be considered carefully. Patients positive for human immunodeficiency virus (HIV) represent a transmission risk, but the use of disposable needles (which should be universal) protects against this hazard. One should carefully consider persons with a cardiac pacemaker or transcutaneous stimulator when doing stimulation



• **Figure 19.1** **A**, Commonly used ring electrodes for measurement of median and ulnar sensory nerve conduction studies. **B,** Placement of electrodes for median sensory nerve conduction studies and sensory nerve action potentials obtained on stimulation of the median nerve at the wrist. **C,** Ground electrode; G1, recording electrode; G2, reference electrode. (**A,** Courtesy of Oxford Instruments Medical, Inc., Hawthorne, NY.)



• **Figure 19.2** **A,** Schematic illustration of three normal motor units, "a," "b," and "c." *Note:* Muscle fibers of different motor units are normally intermingled. Below the motor units are action potentials of five individual muscle fibers of a motor unit and its summated motor unit potential. **B,** Myopathic changes in motor unit "a." Of the original five muscle fibers, three have undergone degeneration, thus reducing the size of the motor unit. **C,** Neurogenic transformation of motor unit "a." Anterior horn cell "b" is shown undergoing degeneration, and its two muscle fibers are not innervated by axons of anterior horn cell "a," thus leading to an increase in the territory and size of motor unit "a."

for NCSs. Certain muscles, such as the rhomboids and abdominals, which are sometimes interrogated by NEE in pain patients, and the diaphragm (rarely), carry a risk for infectious peritonitis and pneumothorax, respectively. Beyond placing a needle through an infected site, there are probably no absolute but only relative contraindications to EMG. Extremely anxious patients and some children occasionally require some sedation. Aftereffects are negligible, with rare bruising, although occasionally a highly disturbed, suggestible, or litigious patient may complain of increased pain or disability vehemently.

Functional Physiology

When recording extracellularly, as with EMG, the electrode picks up the action potential as it is conducted through the medium that surrounds the active fiber. The impedance of the external medium is small compared to the impedance of the fiber interior, and hence the voltage of the extracellularly recorded potentials is maximally only 2%–10% of the intracellularly recorded potential changes. The functional unit (Fig. 19.2) in reflex or voluntary activity is the motor unit; a motor unit is the group of muscle fibers innervated by a single anterior horn cell.[7]

Conduction along the fine intramuscular branches of the anterior horn cell axon occurs so rapidly that all muscle fibers in a motor unit are activated nearly simultaneously. The number of muscle fibers per motor unit varies considerably from muscle to muscle; for example, in the gastrocnemius, the motor unit consists of about 1600 muscle fibers, whereas in the small muscles of the eye, there are only 5–10 fibers. The motor units in various muscles cover different areas of the muscle's cross-section (e.g. brachial biceps, 55 mm; rectus femoris, anterior tibial, and opponens pollicis, 8–9 mm). The distribution of fibers is such that fibers

from several different motor units are intermingled, which is why four to six motor units can be identified by EMG from the same intramuscular recording point.[7]

In normal muscle, these single motor unit potentials can be differentiated only during weak voluntary effort. Utilization of sub-maximal effort during the recruitment phase of needle EMG recording and evaluation is critical to allow for the objective assessment of motor unit morphology and recruitment parameters. The potentials from different motor units are recognized by their frequency of discharge, which varies for each motor unit (some are more or less excitable). The various potentials often differ in appearance because of the differential distance of the recording electrode from the individual fibers of the activated motor units and the differential distribution of the motor end plates in the several units within "range" of a concentric or single needle electrode in one position in the muscle.[7]

An upward deflection on the oscilloscope is considered electrically negative, and a downward deflection is considered electrically positive. Motor unit morphology will vary as a direct consequence of distance from the recording electrodes. Only motor units with an initial negative deflection and a rapid rise time should be evaluated in terms of amplitude, duration, and presence of an abnormal number of turns or phases. These parameters are critical in evaluating potential neuropathic and myopathic processes and help determine the acuity versus chronicity of the suspected disorder.[4,5,7]

Physiology of Nerve Conduction

The cell membrane (axolemma) of a nerve axon separates the intracellular axoplasm from the extracellular fluid. The unequal distribution of ions between these fluids produces a difference in potential across the cell membrane. This resting potential is about 70 mV and is negative on the inside with respect to the outside of the cell membrane. When a nerve fiber is stimulated, it causes a change in the membrane potential; a rapid but brief flow of sodium ions occurs through ionic channels inward across the cell membrane and gives rise to an action potential.[5,7]

The way in which an action potential is conducted along an axon depends on whether the axon is myelinated or unmyelinated. In a myelinated fiber, the action potential is regenerated only at the nodes of Ranvier, resulting in action potentials that "jump" from node to node or saltatory conduction. The velocity of nerve conduction depends on the diameter of the myelinated fiber. Small myelinated fibers may conduct as slowly as 12 m/s, whereas large motor and sensory fibers conduct at a rate of 50–70 m/s in humans. In an unmyelinated fiber in humans, the conduction rate is about 2 m/s.[5,7]

Several factors affect conduction velocity other than whether the axon is myelinated:

Temperature of the limb (low temperatures decrease conduction velocity).

Age of the patient (infants have slow conduction velocities and older adults have increasingly slowed conduction velocities).[5,7]

Height of an individual (increased height may increase the internodal distances of the nodes of Ranvier and potentially lead to erroneous interpretation of numeric data).[8]

Basic Electromyography Examination

EMG must be combined with clinical examination of the patient by the electromyographer. This includes grading of muscle strength and elicitation of muscle stretch reflexes. It is of prime importance for the electromyographer to personally correlate the clinical data and that obtained by EMG. With the understanding that the EMG examination is an extension of the clinical examination, the patient must be evaluated fully, and the problem tentatively assigned to the portion of the anterior horn cell system that seems most likely to be involved. The electromyographer determines the segment or segments of the peripheral nervous system suspected to be involved, and the examination is planned to either substantiate or invalidate the presumptive clinical diagnoses. EDX data that are discordant with the clinical examination are not to be ignored, but rather an explanation and rationale for that data are required, and its significance, or lack thereof, needs to be addressed.

Needle Findings in Normal Muscle

Insertional Activity

When the needle is inserted into a normal muscle, it evokes a brief burst of electrical activity that lasts no more than 2–3 ms after the needle ceases to move. This point is critically important because persistent pressure on the needle can potentially lead to spurious determination of increased insertional activity and possible pathologic condition.[5,7,9] This activity is described as insertional activity and is generally 50–250 mV in amplitude (Fig. 19.3A). These insertional potentials are believed to represent discharges from muscle fibers produced by injury, mechanical stimulation, or irritation of the muscle fibers.

Spontaneous Activity (Activity at Rest)

When the needle is stationary, and the muscle is relaxed, there is no electrical activity present in normal muscle except when the needle is in the area of the endplate (Fig. 19.3B). Two types of endplate "noise" are normal (Fig. 19.3C): (1) low amplitude and undulating, which probably represents extracellularly recorded miniature endplate potentials as a result of the release of individual quanta of acetylcholine, and (2) high amplitude highly irregular intermittent spike discharges, which probably represent non-propagated discharges of single muscle fibers excited by intramuscular nerve terminals irritated by the needle. Any other spontaneous activity at rest is abnormal. An increased duration of insertional activity may be seen with loss of innervation or with the primary disease of muscle fiber.[9] Reduction may occur in patients with myopathies or more advanced degeneration in which muscle tissue has been replaced by fat or fibrous connective tissue.

Voluntary Activity

The voluntary activity of the muscle is analyzed after the muscle is studied at rest (Fig. 19.3D). Electrical activity (termed a motor unit action potential) is noted. A motor unit refers to the number of muscle fibers supplied by one motor neuron and its axon. This number varies from muscle to muscle and maybe as few as 10 to more than 1000 muscle fibers. When a motor neuron discharges, it activates all the muscle fibers of the motor unit.

The force of contraction determines the number of motor units brought into play.[5,9,10] This begins with a single motor unit that fires and can be identified on the screen by its distinctive morphology. As effort is increased, other motor units come into play, which can still be individually discerned and have their own individual morphology and audio representation on the loudspeaker. As the contraction increases, the firing rate of each individual motor unit action potential increases, and the action potential is subsequently joined by other motor unit action potentials,

whose firing rates also increase. This phenomenon is known as recruitment (Fig. 19.4). In normal muscles, the strength of a voluntary muscle contraction is directly related to the number of individual motor units recruited and their firing rate. Analysis of motor units includes (1) waveform, (2) amplitude, and (3) interference patterns.

Waveform

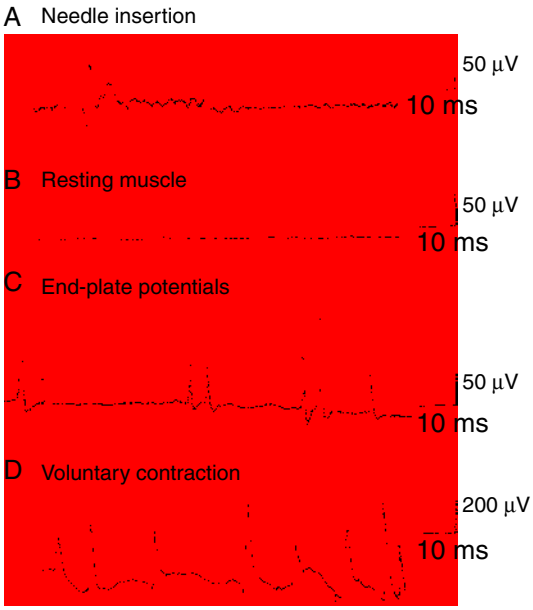
Typical motor units are biphasic or triphasic. The number of phases is determined by the "baseline crossings." Motor units that cross the baseline more than four times are called polyphasic motor units. Polyphasic motor units are determined by the number of baseline crossings plus one. Four baseline crossings plus one equals five, and by definition, that is a polyphasic motor unit potential. Changes in phase not associated with baseline crossings are referred to as turns and can be seen as a consequence of a reinnervated maturing polyphasic motor unit potential after axonal injury in the past. Though occasionally seen in healthy muscle, they do not exceed 15% of the total number of motor units. In some muscles, polyphasic motor units are more prevalent. Polyphasic potentials are a measure of fiber synchrony.[5,7]

Amplitude

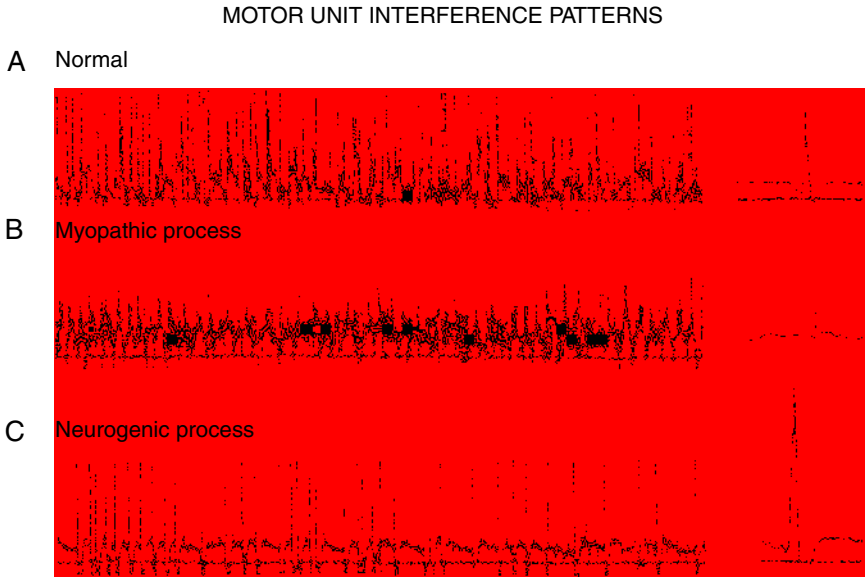
The amplitude depends on the number of fibers in the motor unit, the synchronization of the firing of the fibers in the motor unit, and the type of EMG needle used. Monopolar needles are associated with higher amplitude potentials than bipolar or coaxial needles are. Normal amplitude ranges from 1–5 mV. Because the motor unit is the sum of the action potentials of each muscle fiber of the unit, a large motor unit has a larger amplitude; conversely, a smaller motor unit has a smaller amplitude (Table 19.1).[5,7,10]

Interference Patterns

With maximum voluntary effort, a large number of motor units are brought into play, and their firing rate increases. They tend to "interfere" with each other and are not recognized further as individual units. This gives rise to a situation called an interference pattern (Fig. 19.4). A normal muscle has a "full" interference pattern. With improvement in EMG equipment and the development of A to D conversion, interference pattern analysis is of limited utility. Analysis of sub-maximal contraction allows for evaluation of individual motor units, which in turn offers much richer detail and data in the evaluation of suspected neuropathic or myopathic processes.



• **Figure 19.3** **A,** Trace showing normal insertional activity. **B,** No spontaneous activity in a normal muscle at rest. **C,** Spontaneous endplate potentials. **D,** Normal biphasic and triphasic motor unit potentials during weak voluntary contraction.



• **Figure 19.4** **A,** Full interference pattern on maximum effort in a normal muscle. **B,** Full interference pattern in a myopathic muscle on sub-maximal effort. The number of spikes is greater (each spike represents a motor unit) because of an increase in the firing rate of motor units with early recruitment. **C,** Reduced interference pattern in a denervated muscle on maximal effort resulting from loss of motor units. *Note:* The decreased number of spikes is evident by an increased gap between spikes.

Needle Findings in Abnormal Muscle

Various abnormalities may occur that indicate the presence of muscle dysfunction, which can be neurogenic or myogenic in etiology. The appreciation for the dynamic interplay and synchrony of abnormal EDX findings with a detailed, organized physical exam, buttressed by patient specific historical data, will ease the delineation of radiculopathy, generalized neuropathy, focal neuropathy, or mononeuropathy, or plexopathy.

The following are needle abnormalities in abnormal muscle:

Insertional activity (decreased or increased).

Spontaneous activity (fibrillations, positive sharp waves, CRDs [complex repetitive discharges] or fasciculations) (Fig. 19.5).

Abnormalities in voluntary motor unit activity, especially recruitment (Fig. 19.4).

Abnormal motor unit morphology (e.g. excessive or extreme polyphasia).

NCSs are of value in the following cases:[11]

Determining whether a disease of the nerve is present.

Determining the distribution of neuropathy (e.g. mononeuritis, polyneuropathy, mononeuritis multiplex; this may be a valuable point in the differential diagnosis of the cause of a neuropathy).

Determining at what point in a nerve a conduction block is present and locating an entrapment site.[11]

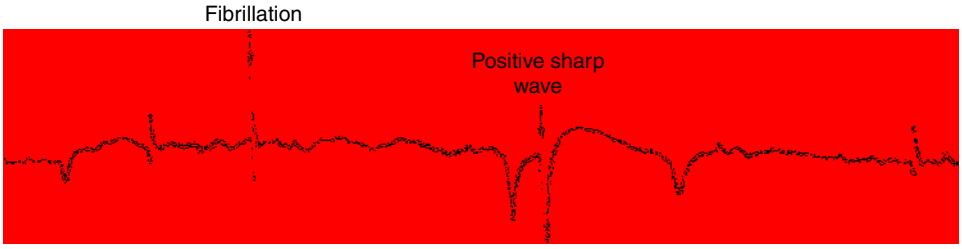
Studying the progress of disease of a peripheral nerve (e.g. Is it getting better? Worse? Staying the same?).

Seeing whether reinnervation of a previously sectioned nerve has taken place.

Establishing in a disease of the myoneural junction (e.g. myasthenia gravis) the fact that conduction along the nerve is adequate or normal.[5,7]

There are a few important limitations to the use of NEE in diseases of muscle and nerve, but particularly muscle. Some disorders may not result in abnormal findings on EMG, including certain congenital conditions and endocrine disorders such as steroid myopathy and polymyalgia rheumatica, an important cause of muscle pain and weakness in an older person. Rarely are the findings specific for a particular type of myopathy within the family of primary muscle disorders.[5,10]

Conduction velocity studies are carried out by inserting a needle electrode into a muscle innervated by the nerve under study or by the use of surface electrodes over that muscle (Fig. 19.6). For example, the first dorsal interosseous muscle may be examined to determine the function of the ulnar nerve (Fig. 19.7). The nerve is stimulated at the elbow in the case of the ulnar nerve, and the latency of the response is determined. The response is generally a spike-like large motor unit action potential. The ulnar nerve is then stimulated in the wrist or the axillary region, or both. The difference in latencies between the

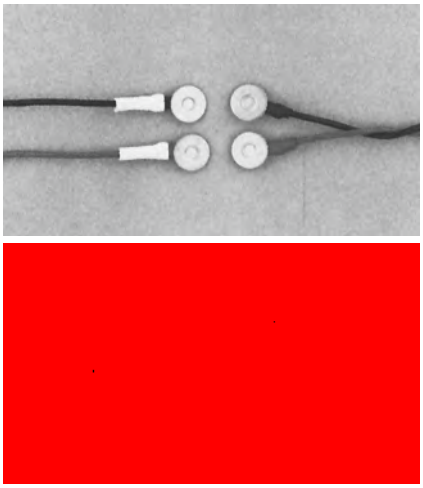


• **Figure 19.5** Positive sharp wave and fibrillation potentials recorded from a denervated muscle.

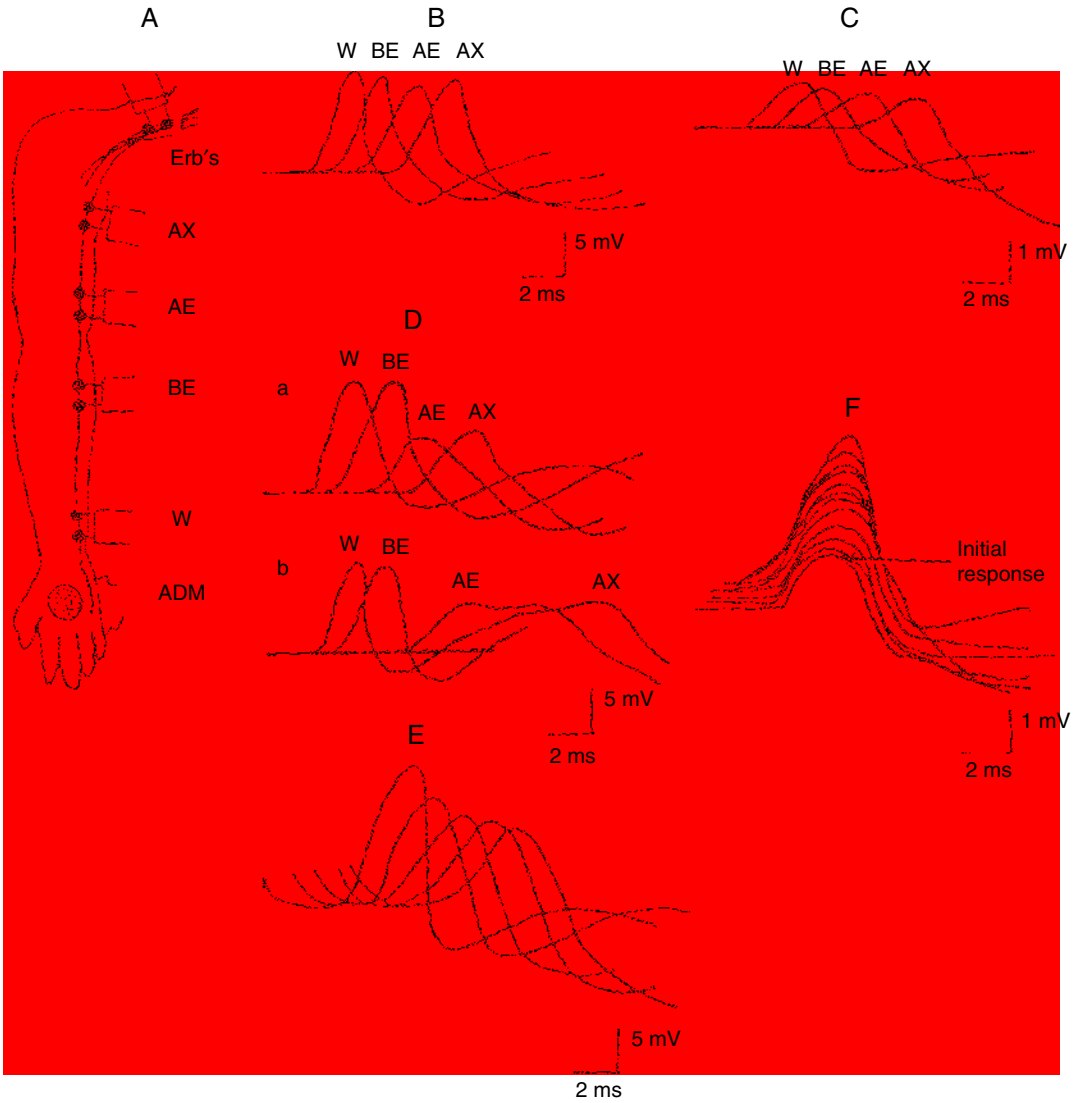
TABLE 19.1 Normal Values for Commonly Tested Sensory and Motor Nerves

Nerves	Amplitude (Avg.)	Distal Latency in msec (Avg.)*	Conduction Velocity in m/sec (Avg.)
Median (sensory)	10–85 μV (20)	2.0–3.7 (3.2)	
Ulnar (sensory)	5–70 μV (15)	1.6–3.2 (2.8)	
Radial (sensory)	10–60 μV (18)	1.7–2.8 (2.4)	
Median (motor)	5–25 mV (8)	2.0–4.0 (3.3)	48–69 (54)
Ulnar (motor)	5.5–20 mV (8)	1.6–3.1 (2.6)	50–69 (55)
Sural (sensory)	3–38 mV (8)	2.3–4.6 (4.1)	41–61 (46)
Peroneal (motor)	2.5–18 mV (4)	2.3–6.0 (4.1)	41–58 (45)
Posterior tibial (motor)	4–38 mV (11)	2.1–6.0 (4.3)	

*Distal latencies are based on standard distance: 13 cm for the median (S), 11 cm for the ulnar (S), 10 cm for the radial (S), 14 cm for the sural (S), 4–6 cm for the median (M) and ulnar (M), 6–8 cm for the peroneal (M), and 8–12 cm for the posterior tibial (M) nerves.



• **Figure 19.6** Disk surface electrodes and a ground electrode are used for the measurement of motor nerve conduction velocity. (Courtesy of Oxford Instruments Medical, Inc., Hawthorne, NY.)



• **Figure 19.7** **A,** Commonly used site of stimulation of the ulnar nerve at the wrist, below the elbow, above the elbow, and at the axilla. The ulnar nerve can also be stimulated at Erb's point in the supraclavicular fossa. **B,** Normal amplitude compound motor action potentials (CMAPs) recorded from the abductor digiti minimi manus following stimulation of the ulnar nerve at these various sites. **C,** Low amplitude CMAPs in a patient with axonal neuropathy. All CMAPs are of the same amplitude but are much smaller than normal. **D,** Decremental response *(a)* and decremental and dispersed response *(b)* on stimulation above the elbow and at the axilla and normal response on stimulation below the elbow and wrist. **E,** Repetitive nerve stimulation of the ulnar nerve at the wrist in a patient with myasthenia gravis. Note the initial normal response and subsequent decremental response at the slow rate (3 pulses/s). **F,** Repetitive nerve stimulation in Lambert-Eaton syndrome. With a rapid rate (20–50 pulses/s), a marked incremental response occurs. Note the very low initial response and the two-fold to four-fold increase following the rapid rate of stimulation. *AE*, Above the elbow; *AX*, axilla; *BE*, below the elbow; *W*, wrist.

two points of stimulation and the distance between the two points of stimulation provide the basis for the calculation of conduction velocity.[11]

F-Wave

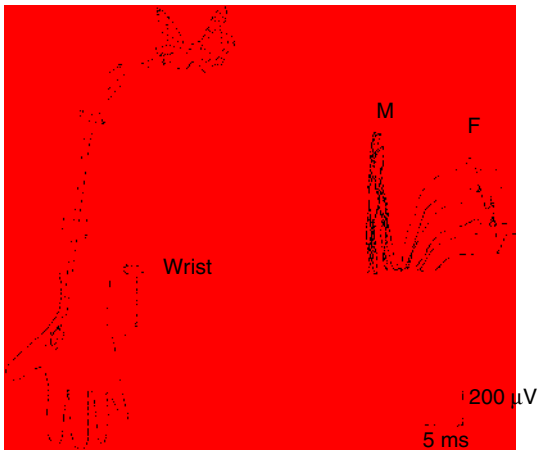
Definition

Motor conduction velocity along the whole axon, including the proximal portions, can be studied by eliciting the F-wave response, a small, late muscle response resulting from backfiring of anterior horn cells. F-waves may be obtained from almost any mixed nerve that can be stimulated, but the median, ulnar, peroneal, and posterior tibial nerves are the most commonly used (Fig. 19.8). If the standard distal motor conduction velocities are normal, but the F-wave value is prolonged, slowing must be occurring somewhere more proximal to the distal normal segment. (The method used to determine F-wave latency varies from laboratory to laboratory; the F-wave value with each successive shock stimulus shows variability of several milliseconds, with some examiners averaging 10, 30, or 50 responses and some taking the shortest of 10, 20, or more responses.) Limb temperature and arm or leg length may also be important to know. Comparison with the opposite limb may be most helpful if that limb is asymptomatic. The determination of F-wave latency can be as simple as accepting the fastest

onset latency after 10 consecutive stimulations or may include analyzing the number of potentials recorded after 10–20 consecutive stimulations and accessing the distribution and spread of the responses. This allows for the development of a scattergram to see where the preponderance of the values reside. In all instances, comparison to textbook standardized onset F-wave latency data is helpful.[12,13]

Pitfalls and Comments

In addition to the variability in F-waves and how they are obtained in different laboratories, many electromyographers overuse (or at least over perform) the F-wave study when proximal slowing in a nerve or nerve root is not even in the differential diagnosis. The most accepted use of the study is for suspected early Guillain-Barré syndrome when the results of the usual studies are still normal, typically in the first 10 days of the illness. It is highly controversial in the evaluation of radiculopathies.[13]



• **Figure 19.8** Consecutive tracings showing M responses and F-waves recorded from the abductor pollicis brevis after stimulation of the median nerve at the wrist.

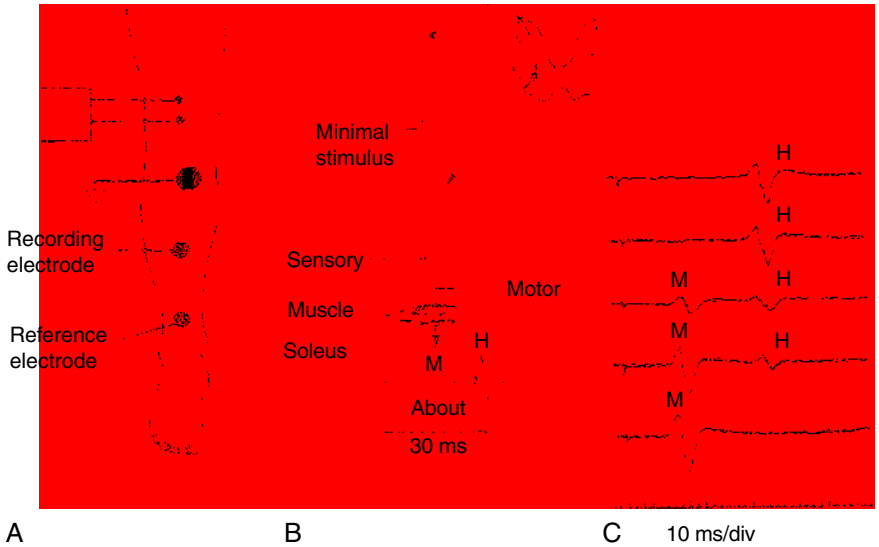
Hoffman Reflex (H-Reflex)

Definition

The H-reflex is obtained by electrostimulation of the posterior tibial nerve in the popliteal space at a slow rate with a long duration and sub-maximal electrical shock; it is recorded with surface electrodes over the gastrocnemius-soleus (Fig. 19.9). The impulse travels up the sensory fibers to the spinal cord, synapses with the α motor neuron, and returns down the motor fibers to the calf muscle. Therefore H-reflex latencies are long, ranging from 40–45 ms. They are carried mostly in the S1 nerve root distribution and cannot be recorded consistently from other muscles. To determine a delay or an asymmetry, one should always study the opposite leg for comparison.[14]

Pitfalls and Comments

The H-reflex is somewhat more useful than the F-wave, but the main reason for the study is to evaluate patients with suspected S1 radiculopathy whose history or findings on physical examination are suggestive, but the EMG is normal. Usually, when an absent H-reflex is noted, which suggests a problem with S1 nerve root conduction, an absent or depressed ankle reflex has already been noted on the physical examination; thus the study is, for many, redundant. Pitfalls occur when the opposite leg is not studied to show a normal H-reflex as a contrast. If the H-reflex is absent bilaterally, it may reflect more generalized disease, such as peripheral neuropathy. Older patients rarely have good H-reflexes as a normal finding. In addition, a unilaterally absent H-reflex with normal findings on needle EMG does not indicate when the injury occurred; the findings may have resulted from



• **Figure 19.9** **A,** Placement of recording electrodes and site of stimulation of the posterior tibial nerve for the recording of the Hoffman (H) reflex from the soleus muscle. **B,** H-reflex pathways. An electrical impulse generated on stimulation of the tibial nerve travels along the sensory axon (afferent) within the spinal cord and along the motor axon (efferent). **C,** Motor response *(M)* and H-reflex *(H)*. Five consecutive traces are shown. Starting from the top, each trace is obtained with increasing stimulus intensity. With minimal stimulus only, the H response is obtained. As the intensity of the stimulus increases, the M response appears, and the H response begins to decrease until it finally becomes unobtainable.

a previous injury. Utilizing prolongation of latency as a determinant of the pathologic condition must be approached with caution. For side to side comparison to be potentially useful, the distance between electrodes, distance between the recording electrode and stimulator, and location of electrodes must be meticulously addressed and recorded.[14,15]

Clinical Correlations of Electromyographic Testing

Electrodiagnostic studies are best for distinguishing neuropathy from myopathy and determining whether a neuropathy is generalized axonal, demyelinating, mixed, focal, or multifocal, thus giving important clues about the cause. Nerve trauma can be monitored serially to determine recovery. Often, a diagnosis of plexopathy or radiculopathy can be made.[4,10,16]

Nerve Trauma

Often after an injury, such as a laceration, the nerve is completely severed. At rest, denervation potentials are recorded in the muscles supplied by that nerve in the form of positive sharp waves or fibrillation potentials, and on EMG, no motor unit action potentials are seen. However, sometimes an injury is incomplete, and the type of nerve lesion is uncertain.[17]

Neurapraxia

Neurapraxia is the mildest form of nerve injury. It consists of loss of conduction without associated changes in axonal structure. The degree of conduction block can be partial to complete. Complete conduction block mimics a complete nerve lesion on physical examination, and in this scenario, NCS lends valuable information regarding the location of the lesion and potentially of greater importance prognosis for recovery. An important physical examination finding suggestive of neuropraxia as opposed to axonotmesis is the preservation of muscle mass with a neuropraxic injury. This form of conduction block often occurs with compressive or ischemic nerve injuries, such as a mild entrapment syndrome or compression (e.g. "Saturday night palsy"). In neurapraxic injuries, focal demyelination occurs.[4,5,7,17]

Axonotmesis

In axonotmesis, a more severe form of nerve injury, the axon is disrupted in its myelin sheath. The neural tube, which consists of the endoperineurium and epineurium, remains intact. The nerve undergoes Wallerian degeneration, with the fragmentation of the axon distal to the site of injury. Motor and sensory paralysis occur along with associated atrophy of the muscles supplied and loss of reflexes. After about four to five days, the distal segments of the nerve become unexcitable. The development of injury potentials, which can include fibrillations and positive sharp waves, proceeds in a proximal to distal fashion relative to the site of injury. Fibrillation potentials may appear as early as two weeks in proximal muscles, with similar findings occurring as late as four to six weeks in distal muscles. The intact neural tube forms a lattice for the regenerating axon, and the prognosis for recovery is generally good, with caveats of age, underlying medical conditions, such as diabetes, and a history of chemotherapy, impacting recovery potential.[4,5,17]

Neurotmesis

Neurotmesis is the most severe form of nerve injury and consists of severe disruption or transection of the nerve. Nerve regeneration and recovery are often incomplete, and surgical reanastomosis may be required. Neuromas may form and are commonly associated with pain. Only serial determinations over time can determine the difference between axonotmesis and neurotmesis.[4,5,17]

Nontraumatic Neuropathies

In a patient with nontraumatic neuropathy, segmental demyelination is generally associated with slowing of NCV and temporal dispersion of evoked responses. With axonal degeneration, however, a reduction in the evoked response amplitudes with mild or minimal slowing of NCV is typical. EMG provides early information regarding reinnervation before clinical recovery is evident. The earliest positive evidence of reinnervation is the appearance during the voluntary effort of motor unit potentials that are of low amplitude in the beginning but are highly polyphasic ("nascent") units. They may be present several weeks before clinical evidence of functional recovery is apparent.[4,5]

Polyneuropathy

EMG and evaluation of nerve conduction are useful in diagnosing polyneuropathy and determining whether the pathologic process is primarily axonal or demyelinating or a combination of the two. Additionally, it helps distinguish predominantly motor versus sensory versus mixed. A diagnosis of polyneuropathy is made when abnormal nerve conduction and EMG findings are bilateral and symmetric.

The following electrodiagnostic findings are characteristic of axonal neuropathy:

Abnormally low or absent sensory nerve action potentials and compound muscle action potential amplitudes.

If a disease process affects the large-diameter axons, some slowing of conduction occurs; the velocity is seldom reduced by 20%–30% of normal. However, fibrillation and positive sharp waves are present in muscles innervated by the affected nerves and are generally worse distally. The feet are more involved than the hand muscles, and the leg muscles are involved more than the arm muscles. Motor unit potentials are decreased in number with deficient recruitment and an incomplete interference pattern. Some motor units have increased amplitude and duration.

In contrast, diffuse demyelinating neuropathy is characterized by a reduction in conduction velocity, usually more than 40% of the normal range. Distal latencies are also prolonged. The sensory nerve action potentials and compound muscle action potentials usually exhibit low amplitudes and temporal dispersion. Needle EMG shows no fibrillations or positive sharp waves unless secondary axonal degeneration is present. In pure demyelinating neuropathy, without associated secondary axonal dropout, there is no denervation of muscle fiber, and clinically, muscle bulk is relatively maintained. Motor units are decreased in number; the decreased recruitment is attributable to conduction block in some fibers. Usually, no significant change in the duration, amplitude, or morphology of motor units occurs, but the number of polyphasic potentials may be increased if the terminal axons have become demyelinated.

Once it has been determined by EMG whether a neuropathy is primarily axonal or demyelinating, one can then consider clinically which neuropathies are diffusely axonal and which are demyelinating. Subacute and chronic diffuse axonal types include most toxic and nutritional neuropathies, uremia, diabetes, hypothyroidism,

HIV infection, Lyme disease, paraneoplastic disease, dysproteinemia, and amyloidosis. Demyelinating polyneuropathies include hereditary motor and sensory neuropathy types I and III, Refsum's disease, multifocal leukodystrophy, and Krabbe's disease. Acute nonuniform demyelinating diseases include Guillain-Barré syndrome, diphtheria, and acute arsenic intoxication, whereas chronic versions include inflammatory demyelinating peripheral neuropathy, idiopathic disease, and neuropathies accompanying HIV disease, as well as various paraproteinemias, dysproteinemias, and osteosclerotic myeloma.[4,5,18]

Mononeuropathies and Entrapment Neuropathies

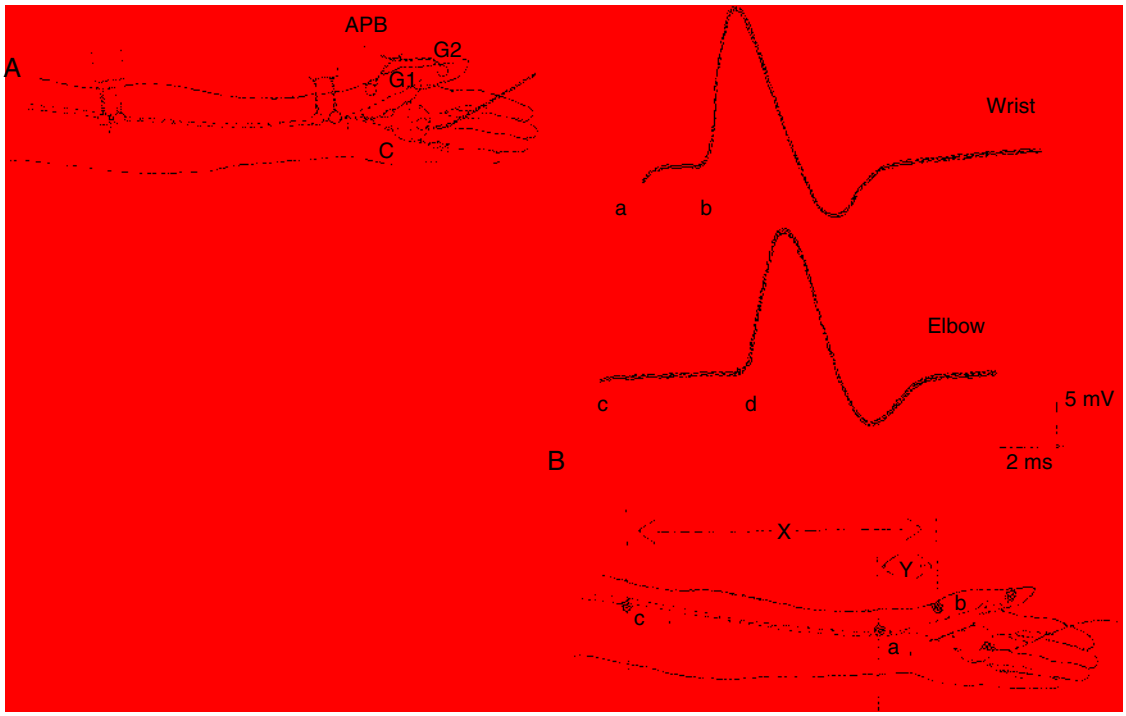
The most commonly involved nerves with entrapment neuropathy are the median, ulnar, radial, common peroneal, and tibial. Entities such as trauma, vasculitis, diabetes mellitus, leprosy, and sarcoidosis can affect any nerve in the body. Electrophysiologic studies are of great assistance in localizing the lesion in the individual nerve and in differentiating mononeuropathy from diffuse polyneuropathy, plexopathy, and radiculopathy.

Median Nerve

The median nerve is most commonly entrapped at the wrist as it passes through the carpal tunnel, but it may also be injured at the elbow where it passes between the two heads of the pronator teres or, less frequently, is compressed by a dense band of connective tissue (the ligament of Struthers immediately above the elbow) (Fig. 19.10). The median nerve is derived from the C6 through T1 nerve roots (lateral and medial cords of the brachial plexus). The diagnosis of carpal tunnel syndrome is made by demonstrating localized slowing of sensory and motor conduction across the wrist as evidenced by prolonged sensory and motor distal latencies.[3] It is critical to understand that slowing by itself does not cause symptoms. Slowing with partial conduction block or complete conduction will cause symptoms. Only when part of the signal fails to reach the target will there be symptoms. In addition, with late changes, there may be denervation in the form of fibrillation, positive sharp waves, and reduced motor units with polyphasia in the hand muscles innervated by the median nerve. The need for reference values for special populations, including people with diabetes and active workers, has been emphasized in a recent AANEM monograph. A recent review also emphasized that carpal tunnel syndrome may represent a focal intracanal condition such as pregnancy, lipoma, an arterial condition, and the hereditary neuropathy of amyloidosis.[19]

Pronator Teres and Anterior Interosseous Syndromes

The pronator teres and anterior interosseous syndromes consist of proximal compression or entrapment neuropathies of the median nerve. Patients with pronator teres syndrome may also have normal distal latency but no evidence of denervation in the median-innervated hand and forearm muscles except for the



$$\frac{\text{DMM}}{\text{PML} - \text{DML}} = \frac{\text{Distance X} - \text{Distance Y}}{\text{Time X} - \text{Time Y}} = \text{m/sec}$$

C

• **Figure 19.10** **A,** Site of stimulation of the median nerve at the wrist and the elbow. **B,** Thenar abductor pollicis brevis compound motor action potentials obtained following stimulation of the median nerve at the wrist and elbow. *a-b*, Motor latency at the wrist; *c-d*, motor latency at the elbow. **C,** Distance and latency measurements for the median nerve and the method used to calculate motor conduction velocity in the segment of the median nerve between the wrist and elbow. *PML*, Proximal motor latency; *DML*, distal motor latency; *DMM*, distance in millimeters.

pronator teres. The anterior interosseous nerve is a motor branch of the median nerve, with its origin just distal to the pronator teres

In anterior interosseous syndrome, a common complaint is deep aching pain in the forearm.

Ulnar Nerve

The ulnar nerve is derived from the C8 and T1 cervical nerve roots (medial cord of the brachial plexus). It is usually injured at the elbow but occasionally at the wrist in the canal of Guyon or deep in the palm (silver beater's palsy). EMG helps differentiate C8 and T1 radiculopathies from plexopathy or distal ulnar nerve palsy (Fig. 19.8). When the lesion is in the wrist at the canal of Guyon, usually both sensory and motor fibers are involved, and the amplitude of the sensory nerve action potential and muscle action potential is reduced. Distal sensory and motor latency across the wrist is prolonged, and there is no focal slowing of motor NCV or decrement in compound muscle action potential across the elbow. With a lesion in the deep palmar branch, no sensory abnormality occurs, and all the changes are in the motor distribution distal to the lesion. When the abnormality is at the elbow, there may be localized slowing of NCV across the elbow, often as much as 25%–40% below normal. Normal values may depend on the method used (arm straight vs. arm bent). The sensory potential may be affected, as may EMG findings in the ulnar hand muscles.[11]

Radial Nerve

The radial nerve is a continuation of the posterior cord of the brachial plexus and receives fibers from the C5–C8 cervical roots. It is usually involved at the spiral groove of the humerus, often secondary to a humeral fracture. With a lesion at the spiral groove, the triceps muscle is noted to be spared on EMG, but the brachioradialis and all the extensor muscles of the forearm are involved. An isolated superficial radial nerve palsy sometimes occurs at the wrist, with the only abnormality being in the radial sensory nerve action potential.[4]

Posterior Interosseous Syndrome

The posterior interosseous nerve syndrome (sometimes known as complicated lateral epicondylitis) is caused by entrapment of this branch of the radial nerve at the arcade of Fröhse between the two heads of the supinator. EMG shows the involvement of the extensor carpi ulnaris, extensor digitorum longus, extensor pollicis longus, and extensor indicis with sparing of the more proximal supinator and extensor carpi radialis longus and brevis. Sensation is unaffected.

Common Peroneal Nerve

The common peroneal nerve is derived from the L4 through S1 roots but primarily from L5. It may be compressed at the head of the fibula. Peroneal NCSs show reduced compound action potentials, as recorded from the extensor digitorum brevis on stimulation above the fibular head and normal compound action potentials below the fibular head and at the ankle.

Posterior Tibial Nerve at the Ankle

The posterior tibial nerve is derived from the L4 through S3 roots and may be compressed in the tarsal tunnel. NCSs show prolongation of the distal motor and sensory latency of the tibial nerve. A side-by-side comparison of mixed plantar nerve amplitudes and motor amplitudes to the adductor hallicus (AH) and abductor digiti quinti pedis is imperative to avoid over interpretation of the data. Needle EMG of the AH and abductor digiti quinti (ADQ) pedis is required to establish the diagnosis of this rather rare entity.

Sciatic Nerve

The sciatic nerve arises from the L4, L5, S1, S2, and S3 nerve roots. Piriformis syndrome is secondary to the entrapment of the sciatic nerve by the piriformis muscle as it passes through the greater sciatic notch.[20] A theoretical "hallmark" finding on EDX is the prolongation of F-wave latency with certain leg positions; however, as previously noted, slowing does not cause symptoms unless it is associated with an element of conduction block and functional axonal dropout. Detailed needle EMG evaluation will typically reveal that the more common cause is lumbar radiculopathy involving the L5 nerve root or S1 nerve root. The isolated finding of F-wave latency prolongation when noted is of unclear significance at best, regardless of the positioning of the leg. A lesion of the sciatic nerve is defined and localized by a detailed needle examination of muscle in the lower limb.

Other Uncommon Neuropathies

There are numerous potential mononeuropathies, including those involving the long thoracic nerve, dorsal scapular nerve, suprascapular nerve, musculocutaneous nerves, and axillary nerves in the shoulder girdle and upper extremity, as well as those in the pelvic girdle, including the femoral, obturator, saphenous, lateral femoral cutaneous, genitofemoral, ilioinguinal, and superior and inferior gluteal nerves. Needle EMG reveals denervation changes in muscles innervated by individual nerves. NCSs are rarely useful in their evaluation.

Radiculopathies

Radiculopathies are diseases of the nerve roots and must be differentiated from plexopathies and complex individual nerve root lesions. Roots are commonly involved by compression, especially in the cervical and lumbar region. However, they may also be involved in diseases such as diabetes mellitus, herpes zoster, carcinomatous infiltration, and lymphomatous infiltration of nerves, as well as by rare (sarcoidosis) and infectious processes. Determination of motor and sensory nerve conduction is rarely useful because the lesion in radiculopathy is proximal to the dorsal root ganglion and motor conduction studies are usually normal. However, they may be reduced in amplitude if the lesion is severe enough to cause axonal loss. The H-reflex is absent or latency-delayed when the S1 root is involved. Typically, nerve root lesions are identified by abnormal needle examination results in the appropriate paraspinal and limb muscles. Understand that with reinnervation, abnormalities may be fully resolved in the proximal paraspinal muscles as reinnervation proceeds from proximal to distal. As such, the "footprint" of the radiculopathy may only be manifest in the more distal arm or leg muscles, respectively. Because most limb muscles are supplied by more than one nerve root (Tables 19.2 and 19.3), a normal study does not exclude the diagnosis of radiculopathy. However, when the findings on EMG are abnormal, they provide objective evidence of functional impairment in the nerve root and localize the lesion to one or more roots in addition to revealing the severity of involvement.[21]

TABLE 19.2 Segmental Innervation of Commonly Tested Muscles in the Upper Extremity

Muscle	Spinal Segment	Nerve Supply
Cervical paraspinal	C2–C8	Corresponding cervical root
Trapezius	C2, C3, C4	Spinal accessory
Supraspinatus	C5, C6	Subscapular
Infraspinatus	C5	Subscapular
Deltoid (circumflex)	C5, C6	Axillary
Biceps brachii	C5, C6	Musculocutaneous
Brachioradialis	C6, C7	Radial
Flexor carpi radialis	C6, C7, C8	Median
Pronator teres	C6, C7	Median
Triceps brachii	C7, C8	Radial
Extensor digitorum communis	C7, C8	Radial
Extensor indicis	C7, C8	Radial
Flexor carpi ulnaris	C8, T1	Ulnar
Abductor pollicis brevis	C8, T1	Median
First dorsal interosseus	C8, T1	Ulnar
Abductor digiti minimi manus	C8, T1	Ulnar

TABLE 19.3 Segmental Innervation of Commonly Tested Muscles in the Lower Extremity

Muscle	Spinal Segment	Nerve Supply
Lumbosacral paraspinal	L1–S1	Corresponding roots
Iliacus	L2, L3, L4	Femoral
Adductors of the thigh	L2, L3, L4	Obturator
Quadriceps femoris	L2, L3, L4	Femoral
Tibialis anterior	L4, L5	Deep peroneal
Gluteus medius	L4, L5, S1	Superior gluteal
Gluteus maximus	L5, S1	Inferior gluteal
Peroneus longus	L5, S1	Superficial peroneal
Biceps femoris—long head	L5, S1	Sciatic
Biceps femoris—short head	L5, S1	Sciatic
Flexor digitorum longus	L5, S1	Posterior tibial
Tibialis posterior	L5, S1	Posterior tibial
Extensor digitorum brevis	L5, S1	Deep peroneal
Gastrocnemius—lateral	L5, S1	Posterior tibial
Gastrocnemius—medial	S1, S2	Posterior tibial
Abductor hallucis	S1, S2	Posterior tibial
Abductor digiti quinti	S1, S2	Posterior tibial
Tensor fasciae latae	L5, S1	Superior gluteal

Plexopathies

In plexopathies, motor NCSs are useful in excluding a peripheral nerve lesion; otherwise, the findings are normal except that the amplitudes of compound muscle action potentials may be reduced. Sensory NCSs are usually helpful in excluding other causes. Again, needle examination is most helpful, but it requires knowledge of which muscles are supplied by which portions of the plexus.

Anterior Horn Cell Disease

Disorders of the anterior horn cell rarely cause pain except for acute poliomyelitis (acute febrile stage). When diseases such as amyotrophic lateral sclerosis cause pain, the cause is usually multifactorial (spasticity, musculoskeletal, positioning) and not usually discernible using EMG.

Disorders of the Central Nervous System

Findings on EMG are almost always normal in diseases of the central nervous system.

Primary Muscle Disorders

One of the clearest applications of EMG is for differentiating myopathies from neuropathic processes. The differentiation in EMG studies between myopathy and neuropathy should be obvious by needle examination. In myopathy, the potentials are reduced in amplitude and may be very polyphasic, recruit paradoxically (i.e. more potentials seen on the screen than expected for the corresponding amount of effort), and are accompanied by marked signs of irritability. In polymyositis and metabolic muscle disorders, sensory nerve conduction is always normal. The compound muscle action potential amplitude may be low, but otherwise, motor conduction results are normal.[10]

In polymyositis and metabolic muscle disorders (e.g. glycogen and lipid storage disease), muscle pain, cramps, and weakness can occur, and needle EMG may reveal findings of membrane instability and irritability. Unusual diseases characterized by muscle cramping, including stiff-man syndrome (Moersch-Woltman syndrome), simply show muscle contraction and spasms. Conditions with continuous muscle fiber activity (Isaacs-Mertens syndrome) show continuous, low amplitude, fibrillation-type potentials.[10]

EMG findings are commonly normal in myofascial pain syndromes and fibromyalgia.

Usefulness and Limitations of Electromyography

EMG and NCSs are useful in localizing neuromuscular disease sites and providing information about the nature of the process (demyelinating, axonal, primary muscular, radicular) but cannot give the cause (diabetes, Guillain-Barré syndrome, myositis, tumor, ruptured disk).

A normal result does not mean that the patient does not have pain. Electrodiagnostic studies in the EMG laboratory, as usually performed, measure only activity related to the motor nerve fibers, the larger sensory nerve fibers, and the muscles. Sympathetic and small unmyelinated nerve fiber functions are not evaluated by standard electrodiagnostic techniques.

In summary, EDX as a stand-alone test is of limited utility. In concert with a detailed history and a well conducted physical examination, the findings noted on EDX testing become very powerful and helpful in delineating the diagnosis and potentially focalizing the treatment decision pathway.

Key Points

1. Electrodiagnostic tests and/or studies can help elucidate the cause of a problem involving the peripheral nervous system.
2. Electrodiagnostic testing has the potential to introduce data that clouds the picture and adds complicating factors.
3. Failure to appreciate the limitations of electrodiagnostic testing can delay diagnosis or lead to wrong conclusions being arrived at.
4. In the evaluation of a patient with pain, particular caution must be taken to guard against the thought process of "if the test is abnormal, that must be the cause of the problem."
5. Data must be interpreted within the context of the patient, and ideally, the test should be tailored to address questions and concerns that arose from the detailed history and physical exam that preceded the electrodiagnostic study.
6. The utility of EDX in the evaluation of a patient with pain, and more importantly, the limitations and potential pitfalls must always be first and foremost in the mind of the electrodiagnostic physician and referring physician when setting up, performing, and interpreting the data.

Suggested Readings

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20

Radiologic Assessment of Patient With Spine Pain

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Imaging is a significant but not independent component of the multifaceted evaluation of a patient with spine or limb pain. Imaging must be interpreted in concert with the history, physical exam, electrodiagnostic evaluation, and responses to image guided anesthetic or provocative procedures. Imaging alone should not be considered; it can only be understood in its proper context: the individual patient's unique syndrome of pain or neurologic dysfunction.

Pain of spinal origin is extremely common. Low back pain is the second most common cause of symptomatic office visits in the United States.[1,2] The lifetime prevalence of back pain in the United States is approximately 75%,[3] and one-third of United States adults experienced back pain in the previous three months.[1] Advanced imaging is performed in such cases with ever-increasing frequency; the number of lumbar magnetic resonance imaging (MRI) scans among Medicare beneficiaries rose four-fold from 1994–2005.[4] Over 40% of patients with acute low back pain underwent immediate imaging in a private insurance claims database study.[5] In another Medicare-based study of low back pain patients without red flags for systemic disease, nearly 30% underwent imaging (radiography or advanced imaging) within 28 days.[6] In a study in an emergency department environment, the use of advanced imaging (computed tomography [CT] or MRI) for low back pain tripled from 2002–2006.[7] Approximately one-third of Medicare low back pain patients who undergo outpatient MRI studies have received no prior conservative therapy.[8]

Despite this intensity of imaging and the downstream effects of increasing minimally invasive interventions and surgical procedures that flow from them, there is no evidence that patient outcomes are improving. Measures of physical functioning, work/school limitations, and mental health in United States adults with back or neck complaints were similar or worse in 2005 than in 1997.[9] A regional study (North Carolina) demonstrated that the proportion of adults with chronic low back pain causing activity impairment rose from 3.9% in 1992 to 10.2% in 2006.[10] A review article by Chou, Deyo, and Jarvik examined the evidence of inefficient utilization of imaging in back pain patients and the underlying causal forces and mechanisms for initiating improvements.[11] The purpose of this chapter is to foster the rational decision making they advocate in the use of spine imaging, based on evidence, as we in the pain management community seek to improve patient outcomes.

The Goal of Imaging

The primary goal of imaging in patients with spine or limb pain is to identify patients suffering from an undiagnosed systemic process causal of the pain/dysfunction syndrome. This is an uncommon phenomenon. An analysis by Jarvik and Deyo[12] suggests that 95% of low back pain is because of benign processes. In patients presenting to a primary care setting with low back pain, only 0.7% suffer from undiagnosed metastatic neoplasm. Spine infection, including pyogenic and granulomatous discitis, epidural abscess, or viral processes, is present in only 0.01% of subjects. Noninfectious inflammatory spondyloarthropathies, such as ankylosing spondylitis (AS), account for 0.3% of presentations. Osteoporotic compression fractures are the most common systemic pathologic process to present as back pain, accounting for 4% of patients.[12] Imaging seeks to identify the approximately 5% of patients with back or limb pain with undiagnosed systemic disease as the etiology of their pain. A related imaging goal is to characterize and assist in therapy planning in the very small percentage of patients with neural compressive disease resulting in radiculopathy or radicular pain syndromes that fail conservative therapy and require surgical or minimally invasive intervention.

Specificity: Asymptomatic Imaging Findings

The low prevalence of systemic disease as a cause of back pain implies that most imaging studies primarily describe what are often, and inappropriately, termed "degenerative" phenomena. These may include anterior and lateral vertebral body osteophytes, loss of T2 signal in the intervertebral disc, and structural changes of facet arthrosis. Degeneration is a pejorative term implying disease; these changes have no relationship to pain syndromes and correlate only with age. They are best called age or age-related changes. These age changes are typically relatively uniform across the spine, although the lowest lumbar segments are over-represented. Evidence for the lack of specificity of such imaging findings for spine pain syndromes is evident in cadaver studies, imaging studies in asymptomatic populations, and population studies.

Nathan[13] described the presence of anterior and lateral osteophytes in 100% of cadavers at the age of 40 years, whereas posterior osteophytes are present only in a minority of cadavers at 80 years. Hult[14] studied adults with spine radiographs and showed that by

the age of 50 years, 87% will have radiographic evidence of age-related disc change (narrowing of the disc space, marginal sclerosis with osteophytes, vacuum phenomena). In a second study including a cohort of asymptomatic workers, Hult[15] noted radiographic evidence of disc "disease" in 56% of those aged 40–44 years, which rose to 95% in subjects 50–59 years old. With the evolution of more sophisticated spine imaging techniques, this lack of specificity of degenerative findings has not improved. Hitselberger and Witten[16] studied plain myelography of asymptomatic volunteers and noted that 24% showed abnormalities that would have been considered significant in the clinical context of back or leg pain. A study of lumbar spine CT in asymptomatic volunteers by Wiesel and colleagues[17] showed that in patients older than 40 years, 50% had "significant" abnormalities. Similarly, Boden and colleagues[18] evaluated MRI of the lumbar spine in asymptomatic volunteers. In patients older than 60 years, 57% had abnormalities considered significant in an appropriate clinical setting. Jarvik and colleagues[19] studied a large patient population with MRI. Their study noted that only extrusions, moderate to severe central spinal canal stenosis, and direct visualization of neural compression were likely to be significant and would separate patients with pain from asymptomatic volunteers. Disc protrusions, zygapophysial joint (z-joint or facet joint) arthrosis, and anterolisthesis or retrolisthesis were virtually always asymptomatic findings. Imaging studies of asymptomatic volunteers are compiled in Table 20.1.[20–25]

A study by Kanayama[26] in 200 healthy adults (mean age 40 years, with no current complaint or therapy for back pain nor any history of lumbar surgery) segregated lumbar MRI findings by segmental level (Table 20.2). Asymptomatic T2 signal loss and disc herniations were most common at the L4 and L5 segmental levels; this series also had a high prevalence of asymptomatic high intensity zones (HZ) (24% at L4 and L5). More recent studies have addressed the prevalence of disc "degenerative" imaging findings (T2 signal loss, loss of disc space height) in younger populations, primarily in Scandinavian countries; these are MRI population-based studies without regard to symptomatology. Kjaer and colleagues,[27] studying children aged 13 years, found a 21% prevalence of disc "degeneration." In a study of adolescents, Salminen and colleagues[28] found a 31% prevalence of disc "degeneration" in 15-year-olds, which rose to 42% in 18-year-olds. Takatalo and colleagues[29] evaluated 558 young adults aged 20–22 years. Using the five-point Pfirrmann classification of disc degeneration, they noted disc degeneration of grade three or higher in 47% of these young adults. There was a higher prevalence in males (54%) than in females (42%). Multilevel degeneration was identified in 17%.

A 2015 systematic literature review included 33 articles and again found a high prevalence of degenerative imaging findings among asymptomatic individuals, which increases with age.[30] For instance, disc protrusions were found in 29% of asymptomatic individuals who were 20 years old and 43% of those 80 years old. Meanwhile, in the same year, a meta-analysis of 14 different studies meeting inclusion criteria provided some conflicting evidence to the concept that degenerative findings on advanced imaging are likely not clinically relevant.[31] For patients 50 years old and

TABLE 20.1 Imaging Abnormalities in Asymptomatic Subjects

Test	Author (reference), Date	Patients (N)	Age Range (mean)	Disc Herniation	Disc Bulge	Disc Degeneration	Central Spinal Canal Stenosis	Annular Fissure
X-ray	Hult[15] 1954	1200	40–44 55–59			56% 95%		
X-ray	Hellstrom[20] 1990	143	14–25			20%		
Myelogram	Hitselberger[16] 1968	300	(51)	31%				
CT	Wiesel[17] 1984	51	(40)	20%			3.4%	
MRI	Weinreb[21] 1989	86	(28)	9%	44%			
MRI	Boden[18] 1990	53	<60 ≥60	22% 36%	54% 79%	46% 93%	1% 21%	
MRI	Jensen[22] 1994	98	(42)	28%	52%		7%	
MRI	Boos[23] 1995	46	(36)	76%	51%	85%		
MRI	Stadnik[24] 1998	36	(42)	33%	81%	56%		56%
MRI	Weishaupt[25] 1998	60	(35)	60%	28%	72%		20%
MRI	Jarvik[19] 2001	148	(54)	38%	64%	91%	10%	38%

From Maus T. Imaging the back pain patient. *Phys Med Rehabil Clin N Am.* 2010;21:725–766, Table 3.

TABLE 20.2 Segmental Distribution of Asymptomatic Lumbar Age-Related Change

Segment	Disc Herniation	Nuclear T2 Signal Loss	Modic Change	HIZ
L1	0.5%	7%	1%	0%
L2	3.5%	12%	3%	4%
L3	16.5%	15.5%	4%	5%
L4	25%	49.5%	11%	23.5%
L5	35%	53%	10%	24%

Data abstracted from Kanayama M, Togawa D, Takahashi C, et al. Cross-sectional magnetic resonance imaging study of lumbar disc degeneration in 200 healthy individuals. *J Neurosurg Spine.* 2009;11:501–507.

younger, Brinjikji and colleagues found that several MRI findings were statistically significantly more prevalent in those with low back pain than those who are asymptomatic. These included disc bulges, degeneration, extrusions, protrusions, and Modic one changes. Spondylolysis demonstrated a similar higher prevalence in patients suffering from back pain. Panagopoulos and colleagues similarly demonstrated that a change over time in some findings (specifically annular fissure, disc herniation, and nerve root compromise) was twice as common in subjects with low back pain than in pain free controls. However, this higher frequency was not statistically significant.[32] However, as acknowledged by the authors of both studies, such association neither is evidence of causation, nor does it provide prognostic information or specific treatment strategies.

As in the lumbar region, age changes in the cervical and thoracic spine are common, asymptomatic, and increase in prevalence with age. Matsumoto studied nearly 500 asymptomatic patients with MRI; he noted a loss of T2 signal within cervical discs in 12%–17% of patients in their 20s, but in 86%–89% of patients older than 60 years old.[33] Asymptomatic cervical cord compression was observed in 7.6% of patients, largely over the age of 50 years. Similarly, Boden studied 63 asymptomatic subjects with MRI and noted cervical disc "degeneration" in 25% of those younger than 40 years and in excess of 60% of patients older than 40 years.[34] Asymptomatic subjects older than 40 years had a 5% rate of disc herniations and a 20% rate of foraminal stenosis. Teresi studied 100 asymptomatic subjects with MRI and noted asymptomatic cervical cord compression in 7% and either disc protrusion or annular bulge in 57% of subjects older than 64 years.[35] In the thoracic spine, Wood studied 90 asymptomatic patients with MRI.[36] In this population, 73% of the patients had positive thoracic imaging findings, 37% had disc herniations, 53% demonstrated disc bulges, and 29% had asymptomatic cord deformity.

The evidence is deep and overwhelming. The structural spine imaging findings most commonly referred to as "degenerative changes" or "degenerative disc disease," including anterior and lateral osteophytes, loss of T2 signal in the disc, loss of disc space height, disc bulges and protrusions, and facet arthrosis, are ubiquitous and unassociated with pain syndromes; their only association is with age. They can only be avoided by a youthful death. They are not a disease state and are best referred to as normal age change or age-related change. Spondylosis (or spondylotic changes) is an alternative term for these maturational changes frequently used in radiology reports.

A consequence of this high prevalence of asymptomatic age-related changes is that the imager must know the nature of the pain syndrome if he or she is to properly focus on findings significant to the unique patient under consideration. There must be concordance of the imaging finding and the pain syndrome it is postulated to elicit. Imaging cannot prove causation; hence, there is a need for anesthetic and provocative procedures. Communication regarding the nature of the pain syndrome is essential, whether this occurs through a robust electronic medical record, an intake document at the imaging site, or direct interaction of the imager with the patient.

Sensitivity: Physiologic Imaging

There is also a major sensitivity fault associated with spine imaging. Most patient symptoms referable to the spine occur in axially loaded positions, either sitting or standing. A substantial portion of radiographs and most advanced imaging (CT and MRI) are obtained in a recumbent position, removing the effects of axial load and physiologic posture. This may fail to reveal the lesion responsible for the index pain.

There is ample evidence of the effect of axial load and physiologic posture on the biomechanical and structural characteristics of the spine, derived from biomechanical, cadaver, and imaging studies. Lumbar intradiscal pressures are higher when sitting or standing than when in a recumbent position.[37] The cadaver study of Inufusa demonstrated a reduction in the cross-sectional area of the lumbar central spinal canal and lateral recesses in extension, with an increase in flexion.[38] Lumbar neural foraminal cross-section is also diminished in extension and increased in flexion. Fujiwara noted a reduction in the cadaveric lumbar neural foraminal area with side bending or rotation toward the index foramen; an increase in area was observed with side bending or rotation away from the foramen.[39] Studying normal volunteers, Schmid observed a 40 mm^2 reduction in the cross-sectional area of the dural sac at the L3–L4 level with movement from flexion to extension.[40] The lumbar neural foraminal cross-sectional area was reduced by 23% in moving from an upright neutral to an upright extended position. Danielson[41] noted a significant decrease in the dural sac cross-sectional area with axial loading in 56% of subjects, most commonly at L4–L5; this was more common with increasing age. Dynamic reduction in dural sac area with loading was less frequent in normal volunteers than in a population of patients with neurogenic intermittent claudication. Hansson and colleagues identified the ligamentum flavum as the most important

structure resulting in a dynamic reduction in the lumbar central spinal canal area under physiologic loading.[42] Physiologic posture (lumbar lordosis) is likely more important than axial load.[43] Multiple studies in patients with upright imaging have demonstrated the enlargement of lumbar disc bulges or protrusions with axial load, which may be further exacerbated with extension.[44,45] Synovial cysts, which may be provocative of radicular pain syndromes or contribute to neurogenic intermittent claudication, may be undetectable on recumbent imaging when synovial fluid remains in the facet joint space. Upon the assumption of axial load and apposition of the facet articular surfaces, the fluid is forced from the joint space into the cyst, where it may act as a neural compressive lesion.

The cervical spine similarly exhibits dynamic physiologic change with posture and load. Cadaveric studies have demonstrated increased disc bulging and buckling of the ligamentum flavum in cervical spine extension; the ligamentum flavum effect was most significant.[46] MRI studies of patients[47,48] noted an increase in central spinal canal stenosis with both extension and flexion of the cervical spine relative to neutral posture; the decrease was most marked in extension. Cervical neural foramina diminish in cross-section, width, and height in extension and increase in all these parameters in flexion.[49]

In summary, physiologic extension and axial load reduce the area of all lumbar spine compartments; these are increased in flexion. The cervical central spinal canal is diminished in areas in extension more so than in flexion; it is maximal in the neutral position. Cervical foramina increase in all dimensions in flexion and diminish in extension. These dynamic changes constitute the greatest sensitivity fault in imaging: conventional supine imaging may fail to reveal a lesion causal to the patient's symptoms when that lesion is only expressed in physiologic postures.

Several methods have been devised to overcome this sensitivity fault. Radiographs should always be obtained upright; this allows assessment of sagittal and coronal balance in a physiologic posture. Flexion-extension radiographs may detect instability not observed on neutral, upright views, but the yield of diagnostic information is very low. In studies in both the lumbar and cervical spine segments, less than 1% of flexion-extension radiographic studies provided information that was noted on static upright radiographs.[50,51] The cost and radiation exposure are best deferred to a pre-surgical setting, and not during the initial evaluation of the patient's back or neck pain.

Advanced imaging can be performed with axial loading devices on conventional CT or MRI scanners. These devices can improve the sensitivity to the detection of clinically significant central spinal canal compromise.[52] The 2011 North American Spine Society's evidence based guidelines on evaluation and treatment of spinal stenosis suggest axially loaded imaging in the setting of suspected neurogenic intermittent claudication and stenosis unconfirmed by conventional imaging, with a canal diameter of less than 110 mm.[22,53] Willén and colleagues demonstrated that surgical results of cases of occult lumbar spinal stenosis detected only by axially loaded MRI were comparable to those of stenosis observed in unloaded MRI examinations.[54]

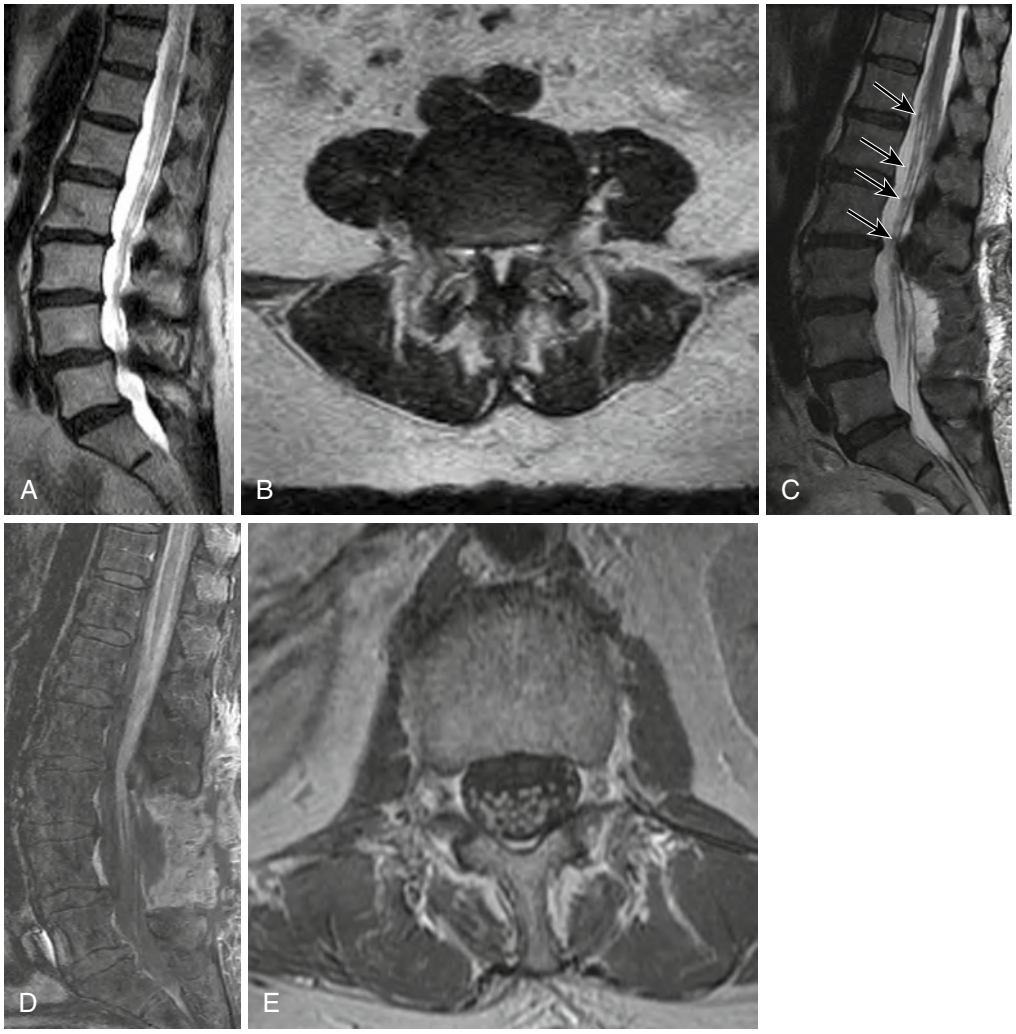
MRI scanning in an upright position—sometimes referred to as dynamic, positional, or kinetic MRI—is now commercially available and widely marketed. Depending on the specific open MRI system, images can be obtained in the standing or seated weight bearing position or during flexion, extension, rotation, bending, or even real-time spinal movement.[55] Performing MRI in a physiologically relevant position offers the possibility of improved sensitivity to detecting central spinal canal, lateral recess, or neuroforaminal stenosis, including spondylolisthesis, as recently reviewed by Baker and MacKay as well as Botchu and colleagues.[56,57] However, studies confirming the clinical and prognostic relevance (specificity) of such increased detection remain lacking.[58] Indeed, no existing literature has demonstrated improved clinical outcomes for treatments based on weight bearing MRI evaluation.[55] A practical challenge is that currently available systems are of low field strength (0.25–0.6 T), significantly lower than standard clinical field strengths (1.5 or 3 T), with an unavoidable reduction in image quality. This reduction in image quality can have important consequences for clinical image interpretation. If current low field strength dynamic systems were applied selectively to cases where conventional imaging failed to demonstrate a correlative lesion causal of the patient's pain, the patient would likely benefit. However, all too often, the cost of these systems or promotion as the best available imaging tool for all spine conditions results in their routine use. This practice could harm patients, as diminished image quality reduces sensitivity to the detection of sinister lesions, which is the primary goal of imaging the back pain patient (Fig. 20.1).

Validity

Spine imaging must be undertaken to fully understand the specificity and sensitivity faults inherent in its use. The ultimate question is one of validity: Does performing an imaging study of the spine segment in question result in improved patient outcomes through a more timely and accurate diagnosis of the process causing the patient's pain? This is well studied, particularly in the application of imaging to the acute presentation of back pain. Chou and colleagues performed a meta-analysis of the six randomized controlled trials (n = 1804) examining the role of imaging in the acute presentation of back or limb pain with no clinical features suggesting systemic disease.[59] They identified no benefit in pain, function, quality of life, or patient-rated improvement in patients undergoing imaging (radiographs, CT, or MRI) at presentation versus those undergoing clinically directed conservative care. Although routine imaging might have been expected to provide reassurance, imaged patients did not have better psychological outcomes.

Carragee and colleagues elegantly demonstrated the lack of utility of imaging in the acute setting in a five-year prospective observational study.[60] A cohort of asymptomatic subjects deemed to be at-risk for back pain resulting from labor-intensive vocations underwent lumbar spine MRI. This patient cohort was followed periodically over the subsequent five years; a subset of these subjects presented to a medical care provider with acute back or leg pain during this five-year period, and a second lumbar MRI was obtained. Less than 5% of the MRI scans obtained during acute presentations with back or leg pain showed clinically relevant new findings; virtually all of the "positive findings" noted on the images at the time of presentation with back/leg pain had been present in the baseline data obtained when the patient was asymptomatic. Only direct evidence of neural compression in patients with a corresponding radicular pain syndrome was considered useful imaging information. Of particular note, psychosocial factors, not the morphology seen on imaging, were the best predictors of the degree of functional disability caused by back or leg pain.[60]

A study by Modic,[61] also in the acute presentation of low back pain or radiculopathy, showed no relationship between the extent of disc herniations and presenting signs or symptoms. The type,



• **Figure 20.1** Diminished sensitivity of low field strength upright MRI to sinister lesions. A 74-year-old female presented with bilateral lower extremity weakness and pain with a low field strength upright MRI from another institution. Sagittal T2 image **(A)** and axial T2 image **(B)** at the L4 level show degenerative spondylolisthesis at L4 with central spinal canal compromise. She underwent an L3–L5 decompression without change in symptoms. A 1.5 Tesla MRI performed three weeks postoperatively demonstrated nodularity *(arrows)* in the cauda equina on a T2 sagittal image **(C)**. Gadolinium-enhanced fat-saturated T1 sagittal **(D)** and axial **(E)** images demonstrate diffuse leptomeningeal metastases from breast cancer. She died in two months. A high quality preoperative MRI would have likely led to the diagnosis and avoided an unnecessary operation. *MRI,* Magnetic resonance imaging. (From Khalil JG, Nassr A, Maus TP. Physiologic imaging of the spine. *Radiol Clin North Am.* 2012;50:599–611.)

size, or location of a herniation at presentation, or change in size or type over time, did not correlate with clinical outcomes. MRI imaging characteristics did not have measurable value in planning conservative care. The study emphasized that surgical decisions must be made on clinical grounds, given the inability of imaging to predict outcomes. The Modic study, like that of Carragee, demonstrated that psychosocial factors predict functional disability better than imaging parameters.[61]

Although the depth of evidence regarding the inability of imaging to improve outcomes in back and limb pain patients is most profound in the acute setting, it applies more broadly. Chou and colleagues[11] explored the seemingly counterintuitive finding that routine imaging does not lead to better back or limb pain outcomes. This lack of utility can be attributed to the favorable natural history of back and limb pain, the low prevalence of sinister disease as causal of back pain, the weak correlation between imaging findings and symptoms (the specificity fault), and the minimal impact of imaging on clinical decision making. Given the demonstrable modest utility of imaging, the decision to undertake this path must be a carefully reasoned one.

Imaging Risk/Benefit

The decision to proceed with any medical test or procedure should be preceded by a consideration of likely benefit weighed against risk or actual harms. There are benefits to be derived from imaging. Foremost, imaging may suggest the diagnosis of previously unsuspected systemic disease. In patients with a radicular pain syndrome or radiculopathy that has not responded to conservative therapy, imaging may supply invaluable information that allows planning minimally invasive or surgical procedures. Negative imaging could also be valuable in providing reassurance that there is no sinis-

ter disease present and stopping further workup in appropriate circumstances. In patients with chronic pain syndromes, imaging may help to identify the structural or inflammatory cause of such pain. Only when a specific pain generator is identified can a specific therapeutic intervention plan be developed, whether conservative or invasive. Advanced imaging, specifically MRI, can also help plan minimally invasive procedures, such as epidural steroid injections. In this setting, information on anatomy and pathology obtained from MRI allows the interventionalist to rationally plan a procedure in an attempt to maximize its efficacy and minimize patient risk.[62] Although, at a minimum, it is helpful on a case-by-case basis, debate exists as to whether such pre-epidural steroid injection MRI examinations are routinely needed. Based on a randomized controlled trial, the availability of MRI results to the proceduralist performing epidural steroid injections has not been conclusively shown to improve outcomes or significantly affect decision making.[63] However, subgroup analyses of the study cohort suggest that both leg pain score and functional assessment at three months after injection demonstrated greater improvement for those who had injections at optimal levels compared to those in whom the injected location occurred at levels disparate from the MRI findings.[62] Moreover, in one-third of patients for whom the MRI was withheld, an injection different than what would have been recommended if MRI results were available was performed.[62,63] We (the authors of this chapter) do support the use of preprocedural MRI when epidural steroid injections are being considered.

There are direct harms and potential risks associated with imaging, which must be balanced against potential benefits. These include radiation dose, cost, the labeling effect, and the downstream risk of provoking minimally invasive or surgical interventions of dubious efficacy.

Radiation dose in radiography, CT, or CT/myelography, and nuclear medicine studies, constitutes direct patient harm. Radiation exposure from radiographs, CT, and nuclear medicine studies carries a cumulative risk of neoplasm induction. This risk becomes particularly problematic when serial studies are performed. The biologically effective absorbed radiation dose is measured by the Sievert (Sv); in North America, the average annual natural background exposure is approximately 3 mSv.[64] A frontal and lateral chest radiograph is often considered the common currency of radiation exposure, incurring a dose of approximately 0.1 mSv. A three-view lumbar spine radiographic series is then worth approximately 15 chest radiographs or 1.5 mSv; cervical spine radiographs incur a dose of 0.2 mSv. A dose of 6 mSv is typical for a lumbar spine CT scan, a value of 60 chest radiographs. Cervical spine CT incurs 2 mSv or 20 chest radiographs. A technetium bone scan has a dose of 6.3 mSv. The cumulative radiation exposure creates real harm; the 2.2 million lumbar spine CT scans performed in the United States in 2007 were projected to result in 1200 future cancers.[65] Although less radiation intensive, lumbar radiography is performed much more frequently than CT and contributes nearly five-fold the cumulative radiation burden to the United States population.[66] The average annual radiation exposure from lumbar radiographs is 75 times that of chest radiography.[66] Radiation risks of spine imaging are made more significant by the necessary inclusion of radiosensitive tissues, the gonadal structures in the pelvis, and the thyroid in the neck.

Imaging studies of the spine are costly. In the United States, the medical imaging community incurs more than $100 billion of societal cost per year. The 2020 Medicare reimbursements[67] for lumbar spine imaging include radiographs: $42; non-contrast CT: $172; CT-myelogram: $504; non-contrast MRI: $241; whole-body positron emission tomography (PET)/CT: $1621; and bone scan with single-photon emission CT (SPECT): $340.[67] Nominal fees are typically three to five times the Medicare reimbursements. It is easy to appreciate how quickly imaging costs can accrue.

The labeling effect refers to the inevitable identification of age-related change, usually described as "degenerative change" or "degenerative disc disease" on imaging studies obtained in the evaluation of back or limb pain. The patient may then perceive that he or she suffers from a degenerative spine condition; the term "degenerative" has only negative connotations. Fearing further damage to their "degenerative" spine, they may give up favorite activities and exercise, resulting in deconditioning and contributing to depression. These fear-avoidance behaviors can be a major impediment to recovery. In a study in which back pain patients were randomized to either receiving or being blinded to the results of their MRI imaging, those who were privy to the results (which were all benign) had a lesser sense of wellbeing.[61] A study of subacute or chronic back pain patients showed that those who underwent spine radiography reported more pain, had a diminished global health state, and consumed more follow up care than those who were not imaged. These findings emphasize the need for patient education regarding the insignificance of age-related imaging findings; imaging professionals should carefully choose descriptive language in imaging reports and avoid the use of pejorative terms such as "degenerative change."

Finally, and most ominously, imaging may precipitate interventions with little evidence of efficacy and expose the patient to harm. Jarvik and colleagues[68] documented that obtaining advanced imaging (MRI) early in a patient's spine pain syndrome leads to increased surgical interventions despite equivalent pain and disability profiles compared with un-imaged patients. Likewise, Lurie and colleagues[69] examined the dramatic regional variation (12-fold) in the rate of surgical intervention for central spinal canal stenosis. These investigators noted that the rate of surgical intervention correlated directly with the intensity of CT and MRI use. In evaluating subjects with acute job-related back pain, Webster and colleagues noted that undergoing an MRI in the first month of symptoms was associated with an eight-fold increased risk for surgery and a five-fold risk for more medical care consumption than that noted for clinically matched, un-imaged subjects.[70] Even in healthcare settings largely unaffected by fee-for-service incentivization, such as the United States Department of Veterans Affairs, early lumbar spine MRI is associated with increasing utilization, such as surgery.[71] Many of the interventions directed toward spine pain, both surgical and minimally invasive, have only modest, if any, evidence basis. Unfortunately, as evidenced by a recent study by Jarvik and colleagues, even including spine imaging reports, epidemiologic data on the high prevalence of lumbar spine degenerative imaging findings seem unlikely to affect subsequent spine related utilization (further imaging, clinical evaluation, or procedure/surgery). However, subsequent opioid prescriptions may be slightly reduced.[72] As noted by the authors, there may be unmeasured benefits from patients and their providers better being able to interpret the significance of imaging findings.

Imaging Recommendations

Imaging is performed to identify the cause of a patient's back or limb pain. Spine imaging has major specificity and sensitivity faults. The decision to initiate imaging must occur as a reasoned decision, weighing potential benefits against the real harm and

risks. The evidence is clear there is no benefit to imaging in the acute presentation of uncomplicated back or limb pain in the absence of signs or symptoms of systemic disease. These principles are firmly based on evidence and have led to the imaging guidelines promulgated by several scientific societies. A 2015 study by Jarvik and colleagues is an example of a relatively recent investigation that confirms these principles. Based on a prospective cohort of over 5,000 patients aged 65 years or older with a new primary care visit for back pain from 2011–2013, early imaging (radiographs or MRI/CT) in the first six weeks after the index visit was not associated with better outcomes at 12 months.[73]

These guidelines are not new. In 1994, the Agency for Health Care Policy and Research recommended against imaging patients with back pain within the first month of a pain syndrome without signs of systemic disease.[74] The American College of Radiology (ACR) consensus practice guidelines were restated in 2016.[75] Imaging is not indicated in the patient who presents with acute low back pain with or without radiculopathy except in the presence of "red flag" features raising the suspicion for serious underlying conditions, including:

Potential cancer or infection:

- History of cancer
- Unexplained weight loss
- Immunosuppression
- Urinary infection
- Intravenous drug use
- Prolonged use of corticosteroids
- Back pain not improved with conservative management (up to six weeks of medical management and physical therapy)

Potential spinal fracture:

- History of significant trauma
- Minor fall or heavy lift in a potentially osteoporotic or elderly individual
- Prolonged use of corticosteroids

Potential cauda equina syndrome or severe neurologic compromise:

- Acute onset of urinary retention or overflow incontinence
- Loss of anal sphincter tone or fecal incontinence
- Saddle anesthesia
- Global or progressive motor weakness in the lower limbs

A 2007 joint recommendation from the American College of Physicians (ACP) and the American Pain Society stated that imaging should not be obtained in patients with nonspecific low back pain.[76] More recent guidelines/recommendations of other societies, including the Choosing Wisely initiative established by the American Board of Internal Medicine, continue to align with this 2007 recommendation. Imaging should only be performed when severe or progressive neurologic deficits are present or when serious underlying systemic disease is suspected. Furthermore, patients with signs or symptoms of radiculopathy or spinal stenosis should be imaged only if they are candidates for surgical or minimally invasive intervention (e.g. epidural steroid injection). In a further elaboration on these guidelines, the ACP, in its initiative to promote high-value medical care, provided more specific imaging recommendations based on clinical scenarios (Table 20.3).[77]

There is evidence that of the small proportion of subjects with a sinister disease as the cause of their back or limb pain, virtually all have risk factors that trigger imaging under these guidelines. A retrospective study of 963 patients presenting with acute low back pain noted that the eight subjects with neoplasm all had clinical risk factors.[78] In a prospective study of 1170 acute low back pain patients without clinical risk factors, no cases of neoplasm were found.[79] No sinister disease was missed in the absence of clinical risk factors in a subsequent systematic review.[80]

Despite these well-supported, evidence based guidelines, clinical practice in the United States remains greatly divergent from this ideal. By one estimate, between one-third and two-thirds of all advanced spine imaging is inappropriate when measured against existing guidelines.[4] Utilization of spine imaging is accelerating despite a complete

TABLE 20.3 Suggestions for Imaging in Patients With Acute Low Back Pain

Imaging Action and Clinical Situation	Suggestions for Initial Imaging
Immediate Imaging Radiography plus erythrocyte sedimentation rate* Magnetic resonance imaging	Major risk factors for cancer (new onset of low back pain with history of cancer, multiple risk factors for cancer, or strong clinical suspicion for cancer). Risk factors for spinal infection (new onset of low back pain with fever and history of intravenous drug use or recent infection). Risk factors for or signs of the cauda equina syndrome (new urine retention, fecal incontinence, or saddle anesthesia). Severe neurologic deficits (progressive motor weakness or motor deficits at multiple neurologic levels).
Defer Imaging After a Trial of Therapy Radiography with or without erythrocyte sedimentation rate Magnetic resonance imaging	Weaker risk factors for cancer (unexplained with weight loss or age >50 years). Risk factors for or signs of ankylosing spondylitis (morning stiffness that improves with exercise, alternating buttock pain, awakening because of back pain during the second part of the night, or younger age [20 to 40 years]). Risk factors for vertebral compression fracture (history of osteoporosis, use of corticosteroids, significant trauma, or older age [>65 years for women or >75 years for men]). Signs and symptoms of radiculopathy (back pain with leg pain in an L4, L5, or S1 nerve root distribution or a positive result on straight leg raise or crossed straight leg raise test) in patients who are candidates for surgery or epidural steroid injection. Risk factors for or symptoms of spinal stenosis (radiating leg pain, older age, or pseudoclaudication) in patients who are candidates for surgery.
No imaging	No criteria for immediate imaging and back pain improved or resolved after a one-month trial of therapy. Previous spinal imaging with no change in clinical status.

*Consider magnetic resonance imaging if the initial imaging result is negative, but a high degree of clinical suspicion for cancer remains.

Adapted from Chou R, Qaseem A, Owens DK, et al. Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians. *Ann Intern Med.* 2011;154:181–189, Table 4.

lack of evidence of its effectiveness in improving the outcomes of back and limb pain patients. Chou and colleagues have enumerated the causes of this overutilization: inappropriate patient expectations, direct and indirect financial incentives on the part of providers, defensive medicine, and provider time constraints.[11,76,77] These issues present great challenges to imaging professionals and those who utilize imaging to improve the clinical state of their patients. Solutions will undoubtedly be multifactorial,[81] but the education of the patient, the imaging professional, and imaging consumers would seem to be at the heart of the matter. It is hoped that the evidence presented here will assist in more rational decision making regarding imaging the spine pain patient (Box 20.1).

Clinical decision support tools represent an emerging array of applications for helping providers decide whether to order spinal imaging and, if so, what modality. Electronic templates can be and have been created to assist practitioners in various clinical scenarios, including acute low back pain.[82] The use of such templates can decrease total imaging and MR imaging rates in ambulatory care and emergency department settings, though providers may still have valid reasons for over-riding the decision support tool's recommendation not to image.[83,84] Feedback on evidence based guideline adherence ("report cards" for ordering providers) can reduce outpatient lumbar spine MRI ordering.[85] Such relatively low cost health information technology tools can promote evidence based, high-value, and cost-conscious care for patients experiencing spinal pain.[86] Hopefully, they will be increasingly utilized.

Radiographs

With the failure of clinically directed conservative care and having made a reasoned decision to initiate imaging of the spine pain patient, the choice of imaging modality should, according to the ACR, be based on the working diagnosis, the urgency of the clinical problem, and the comorbidities of the patient.[75] Radiographs are not routinely recommended for acute nonspecific low back pain, because of their inherently low value in making a specific diagnosis. However, radiography is the initial modality of choice for patients with low back pain who have a history of low velocity trauma, osteoporosis, or steroid use, or for those who are elderly (i.e. for those who are suspected of having vertebral compression fractures). Such radiographs should ideally be upright, weight bearing, and include the appropriate spine segment. Radiography is also recommended to evaluate a young patient for AS.[75] The ACR and the ACP are consistent in their recommendations that patients with "red flag" features of recent low velocity trauma, osteoporosis, age greater than 70 years, or chronic steroid use (i.e. possible vertebral compression fracture), or young patients with clinically suspected inflammatory spondyloarthropathy should initially undergo radiographs; advanced imaging (specifically, MRI as the first line) should be reserved for patients with progressive neurologic deficits or a strong clinical suspicion of infection or neoplasm or immunosuppression, or in those with persistent symptoms after six weeks of conservative management.[75–77] Radiographs provide a modest sensitivity screen for sinister conditions, establish spine enumeration, and assess the sagittal and coronal plane balance when performed in physiologic positions.

• Box 20.1 Spine Imaging Principles

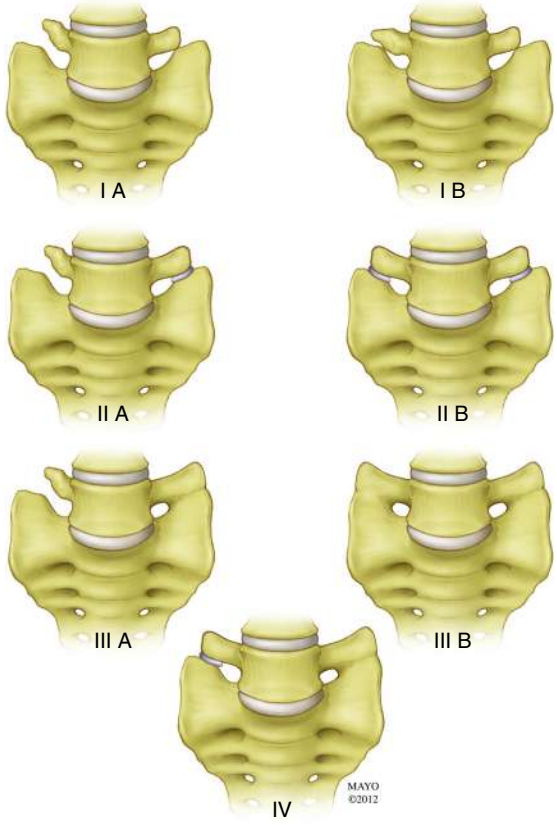
- The primary role of imaging is the identification of undiagnosed systemic disease.
- Spine imaging has a significant specificity fault: a high prevalence of asymptomatic age-related "degenerative" findings.
- Significance of imaging findings depends on concordance: the imager must know the pain/dysfunction syndrome.
- Spine imaging may be insensitive to dynamic lesions.
- No imaging is indicated in the acute presentation of back or limb pain in the absence of "red flag" features.
- The decision to undertake imaging must be a reasoned harms and risk/benefit judgment.
- Imaging correlates poorly with clinical presentation and course.

Spine enumeration is a critical but underappreciated role of radiographs. The typical spine morphology of 24 mobile, presacral spine segments (seven cervical, 12 rib-bearing thoracic, and five lumbar type vertebral bodies) is not uniformly present; deviation can cause confusion in establishing the origin of pain syndromes, or wrong segment minimally invasive or surgical interventions. It can be reasonably assumed in the human species that there are seven cervical vertebrae. Considerable variation in the number and distribution of thoracic and lumbar segments may be difficult to appreciate on MRI alone; radiographs can establish this enumeration and serve as the foundation for subsequent advanced imaging description.

In a study by Carrino and colleagues using complete spine radiographs, 91.8% of subjects had 24 presacral vertebral segments: 4.8% had 23, and 3.4% had 25.[87] Using full spine sagittal MRI localizer images, Akbar and colleagues identified 23 presacral segments in 3.3% of subjects and 25 in 3.3%; these anomalies of spine enumeration were not mentioned in the radiology report in nearly 70% of cases.[88] In Carrino's study, if one considers both anomalous number and distribution (e.g. 13 rib-bearing vertebrae + 4 lumbar type vertebrae) of thoracolumbar spine segments, 10.9% of subjects had nonclassical anatomy.[87] For the spine interventionalist, this implies that these situations are encountered in the procedure room regularly; failure of recognition virtually guarantees wrong segment procedures.

Anomalous segmentation is predicted by the presence of transitional thoracolumbar or lumbosacral vertebral bodies, which may be a source of confusion. Thoracolumbar transitional segments have hypoplastic ribs at the lowest rib-bearing segment; they were present in 4.1% of subjects in Carrino's study.[87] Lumbosacral transitional segments have characteristics of both the L5 lumbar body and the superior sacral segment; their described prevalence ranges from 4%–30%.[89] The Castellvi classification (Fig. 20.2) describes the morphologic types, ranging from an expanded (height >19 mm) dysplastic transverse process (type I), through a pseudoarticulation between the transverse process and sacral ala (type II), to osseous fusion between the transverse process and the sacrum (type III).[90] Type IV denotes the presence of a type II transition on one side and a type III on the other. Unilateral (a) and bilateral (b) subtypes are also described. On lateral radiographs or sagittal MRI images, a transitional segment can be suggested in the presence of a perceived narrow S1–S2 disc, which extends for the entire anterior-posterior (AP) width of the sacral body with parallel endplates and a squared upper sacral segment (Fig. 20.3).[89] The presence of a transitional lumbosacral segment increased by seven-fold the likelihood of an anomalous number of presacral segments. In patients with radicular pain syndromes and lumbosacral transitional anatomy, the pain practitioner must also know the possibility of an extraforaminal nerve entrapment between the enlarged transverse process and sacral ala.

Correlation of pain syndromes with imaging findings can be confounded in patients with transitional anatomy or anomalous segmentation. It is best to consider that radicular innervation



• **Figure 20.2** Castellvi Classification of lumbosacral transitional segments.

patterns remain relatively constant when counted caudally from the skull base, but the skeletal anatomy may change about them. For example, the 26th nerve (eight cervical, 12 thoracic, five lumbar, first sacral nerves) from the skull base most commonly innervates the medial head of the gastrocnemius and the soleus muscles, the basis of the S1 radicular pain pattern. A patient with 25 presacral vertebral segments may exit under the pedicle of the lowest lumbar type vertebral body, creating confusion for the unwary practitioner (Fig. 20.4). There is also variation in typical innervation patterns in the presence of transitional anatomy, which may introduce further localization challenges. Only meticulous attention to spine enumeration, best provided by plain radiographs, sometimes supplemented by total spine MRI localizer images, will protect the spine pain patient and interventionalist from wrong segment invasive procedures (Box 20.2). Sometimes, available chest or spinal radiographs or CT examinations of the chest/abdomen/pelvis or thoracic/lumbar spine can be similarly useful in establishing enumeration.

When radiographs are obtained, they should be upright, weight bearing images. Only in a physiologic posture can one assess sagittal and coronal balance (Fig. 20.5). Upright radiographs demonstrate more thoracic kyphosis and lumbar lordosis than do recumbent images.[91] Weight bearing images may also demonstrate instability, most commonly L4–L5 degenerative spondylolisthesis, which would be occult on recumbent films.[92] Radiographs can be complementary to and provide further information than MRI. For instance, spondylolisthesis is often more pronounced on an upright radiograph than MRI, with the latter potentially underestimating the degree of listhesis and associated central spinal canal narrowing. In spinal deformity patients, the exacerbation of spinal curves with weight bearing can be dramatic. Flexion-extension radiographs in the lumbar or cervical spine are not indicated as part of an initial imaging investigation. There is no role for oblique radiographs of the spine. In the lumbar region, they double the gonadal dose and do not provide useful information that will affect clinical decision making.[92] Cervical spine oblique views similarly serve only to irradiate sensitive tissue (thyroid, lens of the eye) without clinical benefit.

Advanced Imaging Modalities

When patients who are deemed to be interventional candidates have low back pain lasting over six weeks despite conservative management, advanced imaging (CT, MRI, nuclear medicine) may be obtained. MRI is considered the first line in those with radiculopathic symptoms and in patients with severe or progressive neurologic deficits on presentation and red flag features raising suspicion for a serious underlying condition.[75] CT has undergone a revolution since the early 2000s with the advancement of multidetector technology. A data set for the lumbar spine can now be obtained in a few seconds, eliminating motion artifacts and dramatically improving patient tolerance. This data set can then be reconstructed in any plane without losing spatial resolution or additional radiation exposure. CT provides superior imaging of cortical and trabecular bone when compared with MRI. CT may be necessary to characterize primary bone tumors of the spine. This also helps explain why CT is typically the first line modality used in the acute trauma setting for fracture identification, especially in high energy trauma or other settings meeting the high-risk criteria for potential vertebral injury.[75] CT is also excellent at depicting osseous structural problems such as spondylolysis, pseudarthrosis, fracture, scoliosis, and stenosis, and in the postoperative evaluation of bone graft integrity, surgical fusion, and instrumentation.[75] In addition, CT provides reasonable contrast resolution and can identify root compressive lesions, such as disc herniations or characterize central spinal canal, lateral recess, and foraminal compromise, in most cases. CT cannot typically identify intrathecal pathology and is less sensitive than MRI in the detection of early inflammatory or infectious processes, neoplasm, or paraspinal soft tissue lesions. Radiation dose must always be considered when employing CT, particularly in young patients or in serial studies. One by-product of the rapid technologic advance of CT is that the literature contains no comparative studies between MRI and the latest generation of multidetector CT scanners in the detection and characterization of disc herniations. When advanced cross-sectional imaging of the spine is indicated, but the patient is not an MRI candidate, CT is an excellent alternative.

MRI has been the dominant spine imaging modality since the 1990s, despite modest technologic advancement in the realm of spine imaging in that time span. MRI has superior contrast resolution and thus the ability to distinguish between soft tissue types, allowing it to detect intrathecal pathology and identify subtle root compressive lesions. Therefore it is the first line modality for those suspected of having spinal cord compression, spinal cord injury, or cauda equina syndrome. MRI also has superior sensitivity in the detection of neoplasm and infection.

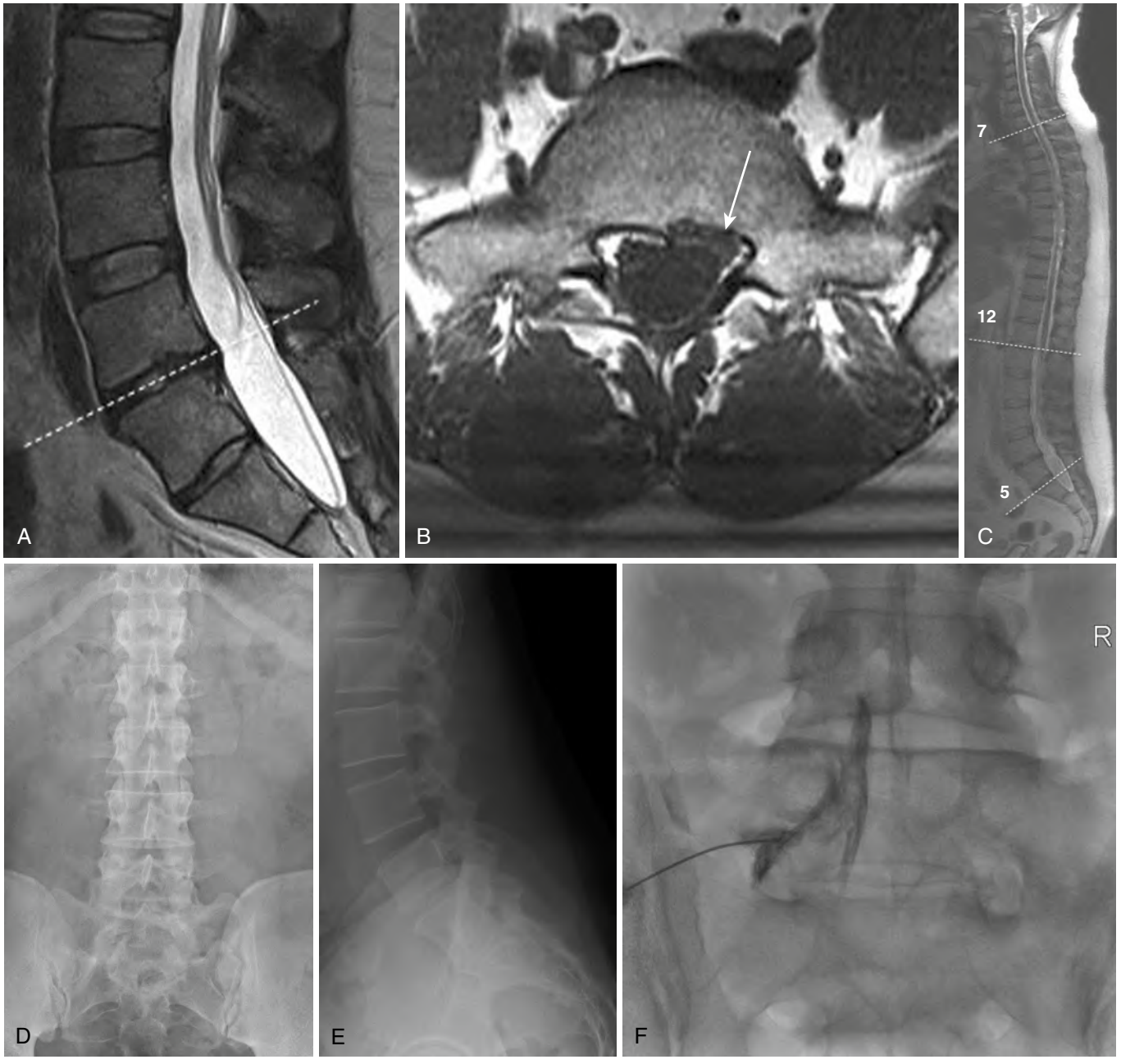
With the use of heavily T2-weighted imaging sequences (short tau inversion recovery [STIR] or fast spin-echo T2 sequences with fat saturation) or gadolinium-enhanced T1-weighted images with fat saturation, MRI can detect the physiologic parameters of edema, hyperemia, and inflammatory change. It

• **Figure 20.3** Transitional segments. Lateral radiograph **(A)** and sagittal T2 magnetic resonance image **(B)** demonstrate typical findings of a transitional segment interspace *(arrows):* a narrow disc space with parallel endplates and normal T2 signal intensity. Castellvi IIa transitional segment is demonstrated in frontal **(C)** and lateral **(D)** radiographs. Note right pseudoarticulation. In another patient, frontal radiograph **(E)** shows a left-sided pseudoarticulation, also seen on the axial computed tomography image (*arrows* in **[F]**). Narrow, parallel endplates are visible in the transitional interspace on the lateral radiograph **(G)**. This patient had axial pain attributed to the pseudoarticulation; this was injected **(H)** with relief of the index pain.

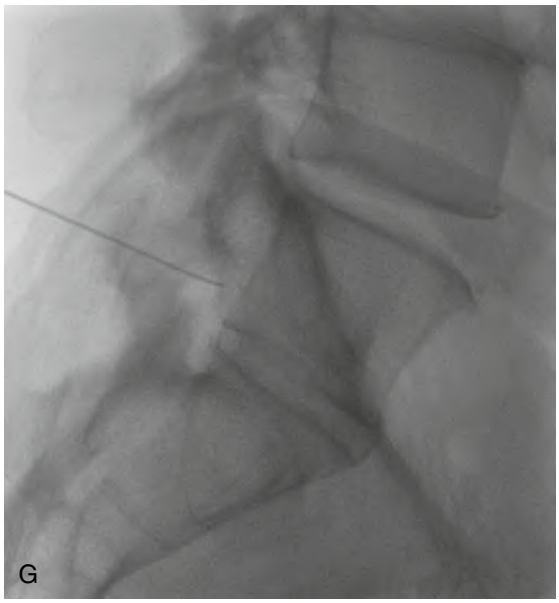
has greater specificity than CT in characterizing the age/acuity of fractures. With gadolinium enhancement, MRI can distinguish between recurrent disc herniation and scarring in the postoperative patient; in this setting, it should be performed without and with intravenous contrast. MRI does not evaluate the cortical bone well. Patient acceptance remains problematic because of prolonged imaging times and up to 10% examination failures caused by claustrophobia; this has decreased as imaging practices have increasingly incorporated both wide bore scanners[93] and/or sedation into a routine offering for MRI (typically with oral benzodiazepines). Open magnets also have improved patient acceptance but at the cost of image quality. Despite advances, including MRI-safe implanted devices becoming more commonplace, a small percentage of patients are MRI incompatible

because of some cardiac devices, spinal cord stimulators, or other implanted devices. MRI remains costly. The sensitivity challenges imposed by recumbent MRI imaging were discussed earlier; the hope is that the engineering challenges of high field strength, weight bearing MRI imaging will be met in the near future.

CT myelography retains a problem solving role in the lumbar spine; especially if a routine CT has not answered the clinical question, it will substitute for MRI in the MR-incompatible patient. CT myelography has superior spatial resolution when compared with MRI but lacks its soft tissue contrast resolution. It can provide an exquisite demonstration of root compressive lesions



• **Figure 20.4** The importance of segmental enumeration. This 36-year-old male who has failed conservative care presents with a left-sided L5 radicular pain pattern involving the lateral thigh, lateral calf, and dorsum of the foot. His magnetic resonance image (MRI) (sagittal T2 **[A]** and axial T1 **[B]** at level of *dotted line*) shows a subtle disc extrusion in the left lateral recess (*arrow* in **[B]**) at the second to last interspace. The lowest-most disc appears transitional. MRI scout **(C)** image demonstrates 24 presacral segments. Frontal and lateral radiographs (**D** and **E**) may suggest five lumbar vertebrae on cursory examination. Careful counting at fluoroscopy noted 11 rib-bearing vertebrae. T12 has no ribs, and L5 is transitional, Castellvi type 4. The transforaminal epidural steroid injection (**F** and **G**) was performed under the pedicle bearing the dysplastic left T5 transverse process and relieved the patient's pain.



• **Figure 20.4, cont'd** Note **(G)** the typical appearance of transitional disc space. Careful enumeration of every case is the only way to avoid wrong segment interventions.

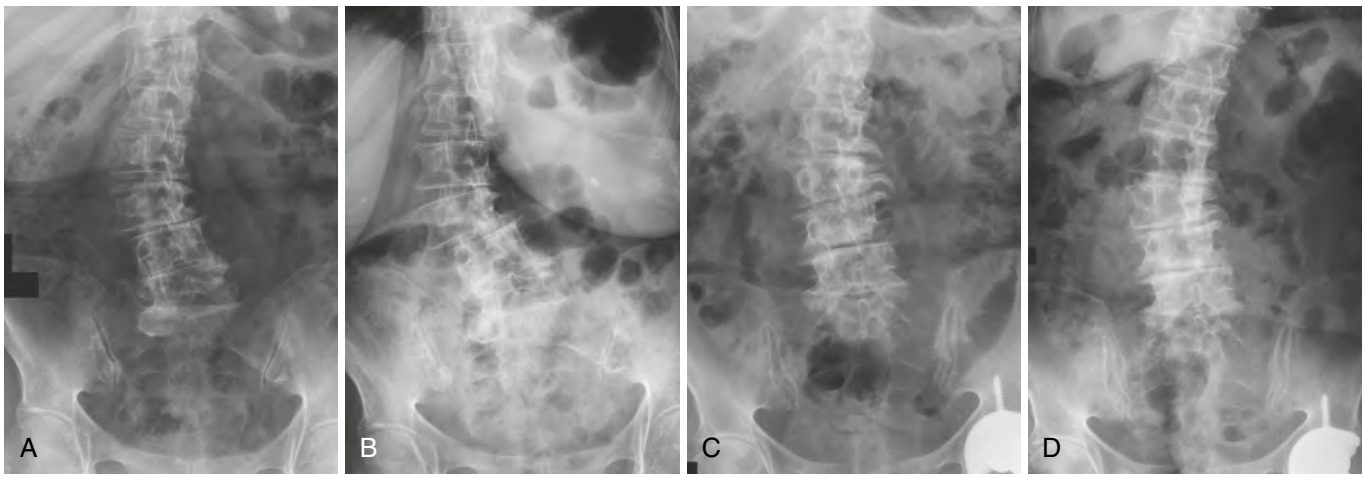
• Box 20.2 Spine Enumeration

- Approximately 11% of subjects will have anomalies of number or distribution of thoracolumbar vertebral bodies.
- Anomalous segmentation is predicted by the presence of transitional thoracolumbar or lumbosacral vertebral bodies.
- Ideally, vertebral numbering should occur from the skull base caudally.
- Practically, the human cervical spine is homologous and can be assumed to have seven segments.
- T1 is marked by the first upward inclined transverse process.
- Meticulous enumeration on every case will prevent wrong segment procedures.

and central spinal canal, lateral recess, and foraminal compromise. In the cervical spine, the superior spatial resolution of CT myelography and its ability to discriminate between bone and soft tissue compressive lesions give it a continuing role. CT myelography is minimally invasive, expensive, operator dependent to a degree, and also requires current CT technology to be maximally useful.

Cone-beam CT, weight bearing myelography holds promise for assessing position dependent pain syndromes, at least in part defeating the sensitivity fault of recumbent advanced imaging.[94] In this technology, arising from rotational angiography roots, the C-arm rapidly rotates about the standing patient who has had contrast introduced into the thecal sac. A flat panel fluoroscopy detector gathers a data set that can be reconstructed in any plane. Soft tissue contrast does not approach that of true CT, and the longitudinal field of view is limited to the length of the flat panel detector. Despite these limitations, the high inherent contrast among intrathecal contrast, the soft tissue structures of the spinal column, and bone allow for a very good depiction of the central spinal canal, lateral recess, and foraminal compromise. This technology will presumably only improve, but it is not in widespread clinical use even at institutions where it is available (Fig. 20.6). A lower-resolution version of this dynamic is multipositional conventional myelography. In a study of 100 patients, Merkle and colleagues showed that compared to supine MRI, 137 additional stenotic segments were diagnosed in 64 patients by standing myelography with extension, suggesting that routine MRI frequently underestimates spinal stenosis.[95]

Nuclear medicine studies are growing in importance in spine imaging. Technetium pyrophosphate bone scans detect increased blood flow and accelerated bone metabolic activity. With the addition of SPECT and SPECT/CT image fusion, significant additional spatial localization of hyperemia and increased metabolic activity are possible. This imaging is traditionally helpful in assessing the burden of metastatic disease but can also be valuable in assessing non-neoplastic inflammatory states such as spondylolysis. SPECT/CT can potentially identify inflammatory synovitis in the facet and sacroiliac joints, which might guide interventions.



• **Figure 20.5** The effect of upright weight bearing radiographs on balance and deformity. Recumbent radiograph **(A)** shows lumbar scoliosis with a rotatory component, which is significantly exacerbated in a subsequent upright radiograph **(B)**. In another patient, the recumbent radiograph **(C)** underestimates the true scoliotic curve seen on an upright radiograph **(D)**. Sagittal and coronal balance can only be assessed on upright, weight bearing imaging.

• **Figure 20.6** Ligamentum flavum redundancy (buckling) on upright myelography (cone-beam computed tomography [CT]). A 66-year-old man imaged for neurogenic intermittent claudication. Conventional myelogram in the lateral plane with the patient in the prone position **(A)** and postmyelogram sagittal **(B)** and axial CT at L4–5 interspace **(C)** with the patient in the prone position show minimal redundancy of the ligamentum flavum *(black arrows)* and mild central spinal canal compromise at the L4–5 level. Cone-beam CT myelography with the patient in an upright position demonstrates a marked increase in ligamentous buckling *(white arrow)* on the sagittal reconstruction **(D)** and complete effacement of the thecal sac on the axial reconstruction **(E)**. (Courtesy of Kent Thielen, MD, Mayo Clinic, Rochester, MN.)

However, validation studies of these techniques against accepted reference standards such as comparative blocks in the facet joints or intra-articular sacroiliac blocks have not yet been conducted. When MRI is not technically feasible, technetium bone scanning can be used to characterize the age of vertebral fractures in selecting patients for bone augmentation. The technetium bone scan, combined with gallium scan, offers sensitivity equal to MRI in the detection of spondylodiscitis. However, these techniques provide less anatomic information and a lesser ability to make a specific diagnosis; MRI may ultimately be necessary to characterize the degree of central spinal canal compromise that may influence surgical decision making. PET or PET/CT scans have an increasing role in assessing the burden of metastatic disease and in selecting lesions for percutaneous biopsy.

Imaging of Axial Pain Generators

Axial pain that may have an imaging correlate derives primarily from the stimulation of nociception of the spinal articulations: the intervertebral disc, the zygapophysial or facet joints, and the sacroiliac joint. More broadly, it may include pain originating from the muscular or ligamentous structures in the supporting architecture of the spine. Axial pain is clinically characterized as constant, dull, deep, poorly localized, and aching, located primarily in the paraspinous region with inconstant referral to the proximal extremities. This is in distinction to the neuropathic pain of radicular character, which is typically sharp, electric, lancinating, and experienced in a bandlike distribution into the more distal extremities. DePalma and Maus have well described the prevalence of axial spine pain generators (Table 20.4).[96,97] Intervertebral disc disruption (IDD) was the most common axial pain generator in this series, followed by the facet joint, the sacroiliac joint, and insufficiency fractures of the spine or pelvis. This work also emphasized the age dependence of these pain sources. Patients with discogenic pain (IDD) were significantly younger than patients with facet or sacroiliac joint pain. As the age increased, the probability of IDD as a pain source decreased, and the probability of facet or sacroiliac pain increased, up to approximately 70 years of age.[96] A later multivariable analysis also showed a gender relationship, with IDD more prevalent in young men.[98] This echoes the earlier work of Schwarzer, who demonstrated that lumbar facet-mediated pain was uncommon in a population of young workers (~15%) but more highly prevalent in an aged population (~32%).[99,100]

Imaging Correlates of Discogenic Pain

The imaging diagnosis of discogenic pain is made challenging by the lack of a pathoanatomic gold standard against which to assess imaging parameters. It is not possible to evaluate a disc, either at surgery or upon histologic examination, and deem it painful. The current most stringent reference standard for the diagnosis of discogenic pain is manometrically controlled provocation discography with normal control levels as documented in the practice guidelines of the Spine Intervention Society (SIS).[101]

However, it is important to observe that examination of the same body of evidence regarding the validity of discography as the reference standard has resulted in diametrically opposed recommendations regarding its use by different physician societies. The SIS,[101] the North American Spine Society,[102] and the American Society of Interventional Pain Physicians[103] accept discography as a useful diagnostic tool in back pain patients and recommend its use. The American Pain Society rejects discography as a diagnostically useful test.[104] A comprehensive review of discography in the journal of the American Society of Regional Anesthesia and Pain Medicine notes that whereas CT discography is the gold standard for the assessment of structural disc alteration, there is no convincing evidence that using discography as a selection tool improves surgical outcomes.[105] Any analysis of imaging findings in discogenic pain patients thus remains based on a reference standard (provocation discography) that is ultimately unproved against a pathoanatomic gold standard. This is further confounded by the evolution of the criteria for a positive discogram since the 1990s.

Although challenging, there is motivation to make the diagnosis of discogenic pain via noninvasive imaging. Discography has historically been considered a minimally invasive and nondestructive test. Recent *in vitro* and *in vivo* evidence has raised concern that disc puncture or discography may contribute to disc dysfunction. Korecki and colleagues[106] noted that in a bovine disc model, single punctures with a 25-gauge needle resulted in biomechanical degradation of disc function with cyclic loading. Carragee and coworkers demonstrated using a 10-year follow up that asymptomatic subjects who had undergone investigational discography showed more degenerative phenomena on imaging than did matched control subjects and incurred more spine related health care, including surgery.[107,108] Discography in these series allowed intradiscal pressures up to 100 per square inch (PSI) and were not performed on back pain patients. Another study, utilizing back pain patients with intradiscal pressures restricted to <50 PSI per SIS Guidelines, did not show any difference in degenerative imaging findings, including disc herniations, in punctured vs. unpunctured discs.[109] Although the clinical significance of these observations remains uncertain, a noninvasive diagnosis is desirable.

The specificity fault inherent in spine imaging was previously discussed: manifestations of disc "degeneration" including loss of T2 hyperintensity, loss of disc space height, and disc contour abnormalities (disc bulges and protrusions) are ubiquitous, often asymptomatic, and primarily represent normal age change (Fig. 20.7). However, in a population of symptomatic patients with suspected discogenic pain, are there imaging findings that correlate with positive provocation discography?

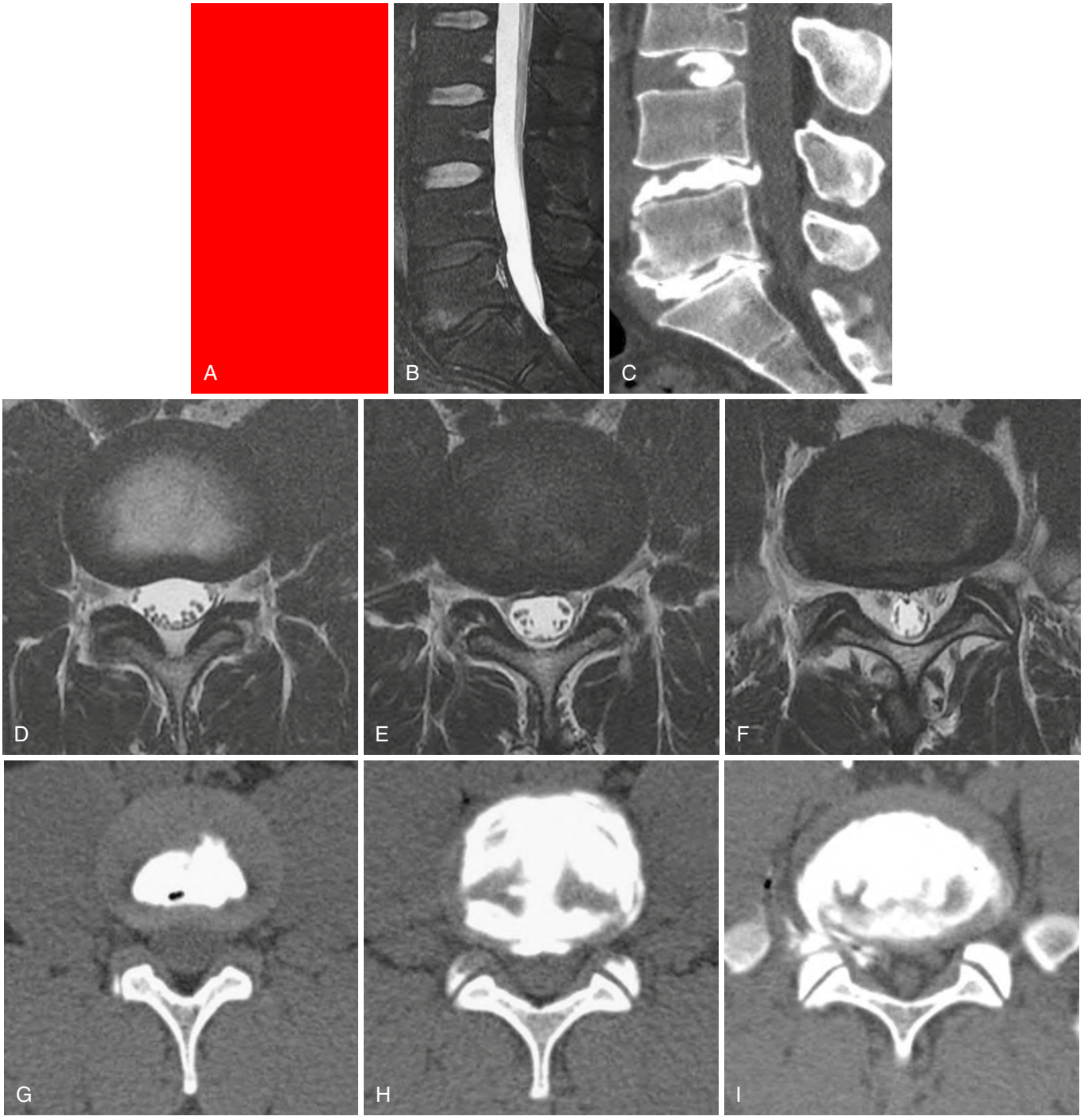
TABLE 20.4 Prevalence of Sources of Axial Low Back Pain, Age Correlation

Pain Source	Prevalence (%)	Mean Age (Std Dev)
Intervertebral disc disruption (IDD)	41.8	43.7 (10.3)
Facet joint	30.6	59.6 (13.1)
Sacroiliac joint	18.2	61.4 (17.7)
Vertebral insufficiency fracture	2.9	79 (11.8)
Pelvic insufficiency fracture	1.8	71.3 (11.7)
Baastrup's disease	1.8	75.3 (4.7)
Fusion hardware	2.9	59.6 (19.4)

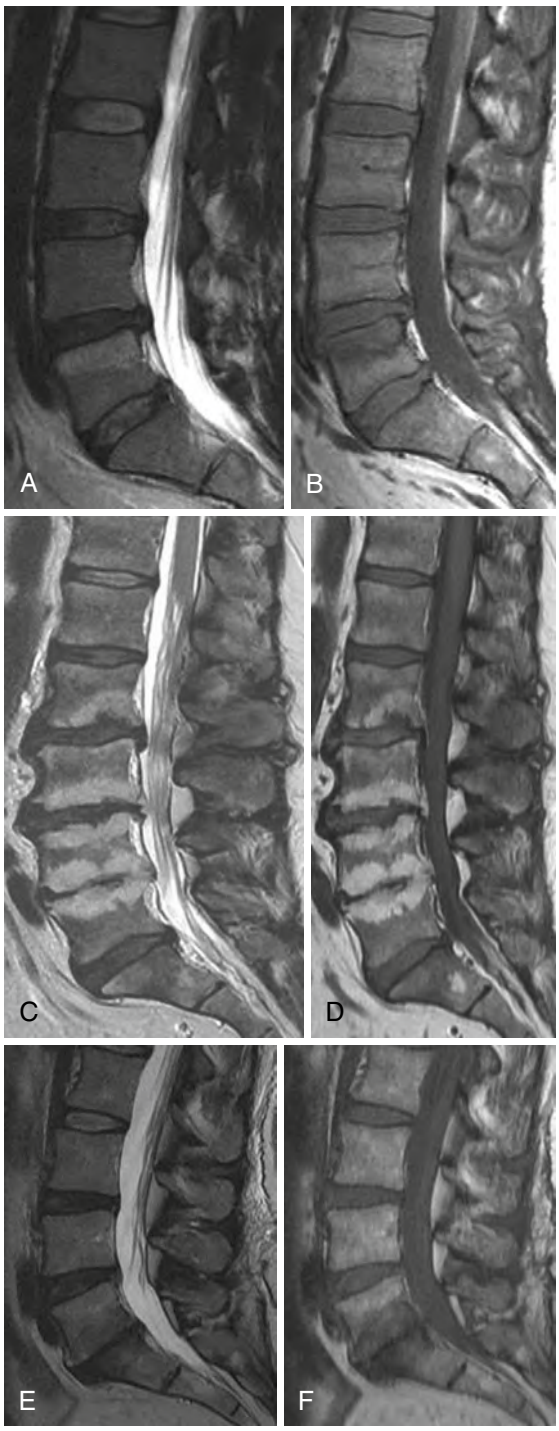
Data from DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med.* 2011;12:224–233.

Modic Endplate Changes

The functional unity of the disc and the cartilaginous endplate is manifested in signal changes within the endplate and adjacent subchondral marrow that accompany nuclear matrix degradation. Endplate marrow changes were originally classified by Modic in 1988 (Fig. 20.8).[110] Type I change represents ingrowth of vascularized granulation tissue into sub-endplate marrow; it exhibits a hypointense T1 and hyperintense T2 signal on MRI and may enhance with gadolinium. Type II change exhibits elevated T1 and T2 signals and reflects fatty infiltration of sub-endplate marrow. Type III change is hypointense on T1 and T2; it correlates with osseous sclerosis. Type I change is thought to represent an active inflammatory state, with type II more quiescent and type III post-inflammatory. Ohtori and colleagues[111] noted elevated levels of protein gene product 9.5-immunoreactive nerve fibers



• **Figure 20.7** Disc Height and Nuclear T2 Signal Loss. Lateral radiograph **(A)** of a 50-year-old male with intractable axial pain. Note the loss of height of the lumbosacral disc, which contains gas. There is slight retrolisthesis of L4 on L5 and L5 on S1. Sagittal fat-saturated T2-weighted MRI **(B)** shows loss of T2 signal in the L4–5 and L5–S1 discs; normal upper lumbar discs. Axial T2-weighted images at L3–4 **(C)**, L4–5 **(D)**, and L5–S1 **(E)** demonstrate normal L3–4 disc, loss of T2 signal in L4–5 with a small central herniation, and a broad bulge at L5–S1. Sagittal CT discogram **(F)** and axial images at L3–4 **(G)**, L4–5 (**H),** and L5–S1 **(I)** show normal L3–4 disc, Grade IV annular disruption at L4–5 and L5–S1 with a leak of contrast from the right posterolateral annulus at L5–S1. Patient had concordant axial pain at L4–5 and L5–S1 with a normal control disc at L3–4. (From Maus TP, Aprill CN. Lumbar discogenic pain, provocation discography, and imaging correlates. *Radiol Clin North Am.* 2012;50:681–704.)



• **Figure 20.8** Modic endplate changes. Modic I sagittal T2 **(A)** and T1 **(B)** images demonstrate elevated T2 and diminished T1 signals involving the superior half of the L5 vertebral body. The histologic correlate of Modic I is vascularized granulation tissue. There are disc herniations at the L3–4 and L4–5 discs. Modic II sagittal T2 **(C)** and T1 **(D)** images reveal elevated T1 and T2 signals in the sub-endplate marrow involving L2–L5. The histologic correlate of Modic II is fatty infiltration. Modic III sagittal T2 **(E)** and T1 **(F)** images show diminished T2 and T1 signals in the sub-endplate marrow about the L5 interspace. The histologic correlate of Modic III is sclerotic bone.

and tumor necrosis factor alpha (TNFα) immunoreactive cells in the cartilaginous endplates of patients with Modic changes. The immunoreactive nerve ingrowth was noted exclusively in patients with discogenic low back pain. TNFα immunoreactive cells were more common in type I endplate changes.

Modic endplate changes do carry an association with low back pain, particularly type I change. Albert and Manniche[112] reported low back pain in 60% of patients with Modic changes and in only 20% of those without Modic changes. Type I change was more strongly associated with low back pain than type II change. Thompson and colleagues examined nearly 2500 discs. Type I change had a positive predictive value (PPV) for positive provocation discography of 0.81, while type II change yielded a PPV of 0.64.[113] Weishaupt and colleagues,[114] with a threshold at 25% of vertebral body height for either type I or type II change, saw no false-positive results (100% specificity). Bogduk compiled the data of six studies examining Modic change of either Type I or II, revealing a specificity of 0.83 (sensitivity = 0.24) and a likelihood ratio of 3.4 as a predictor of positive discography.[115]

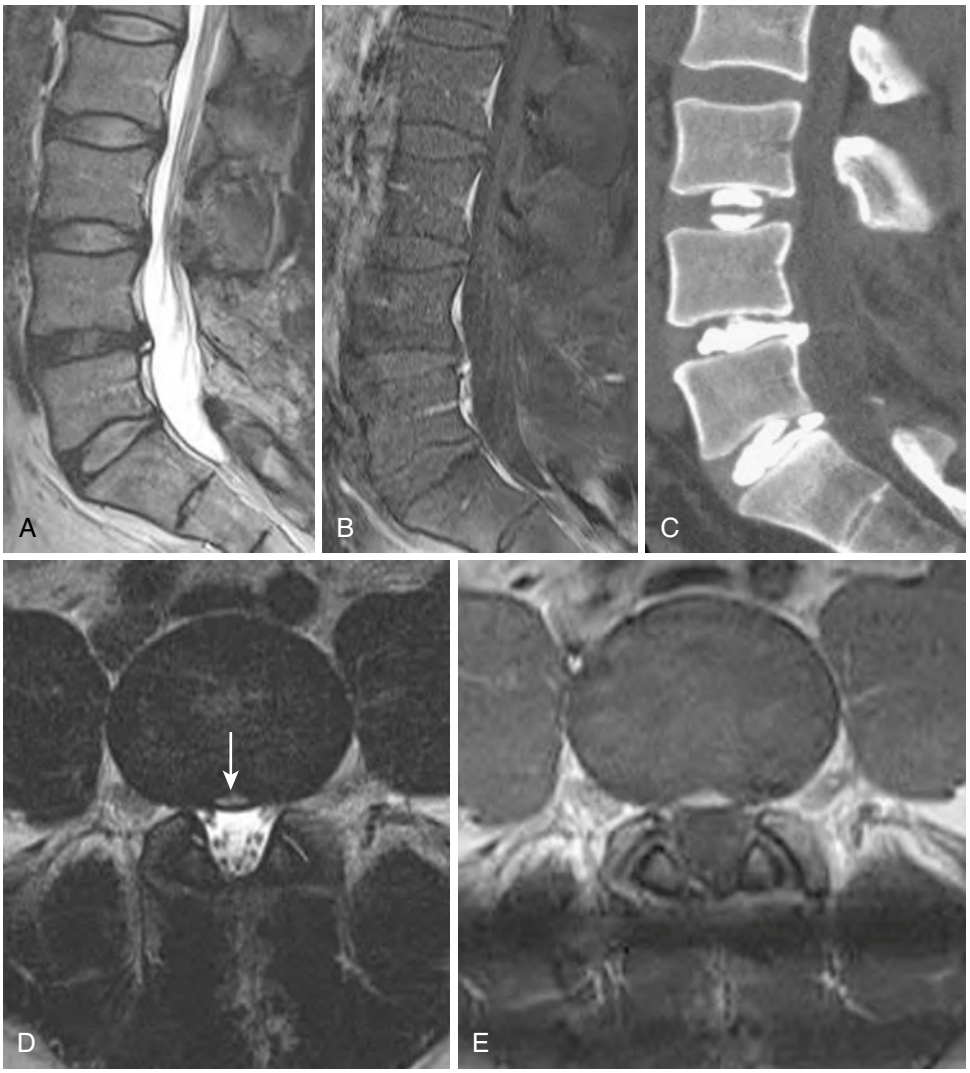
Modic type I change may also be associated with segmental instability. Persistent type I change after fusion surgery raises concern for pseudarthrosis. Patients with solid fusions are more likely to have either persistent type II change or resolution of all marrow abnormality. One caveat about Modic changes is that their detection and classification are heterogeneous across different studies. Among the multiple reasons are a lack of standardized reporting guidelines and technical factors such as magnetic field strength and pulse sequence parameters.[116] As in other disciplines, artificial intelligence will likely play an increasing role in the imaging evaluation of back pain, including the potential for automated detection/calculation of characteristics such as Modic changes and spinal stenosis grades.[117]

High Intensity Zone

In 1992, Aprill and Bogduk described the high intensity zone (HIZ) as an imaging marker of a painful disc at provocation discography (Fig. 20.9).[118] Their definition of the HIZ is a "*high intensity signal (bright white) located in the substance of the posterior annulus fibrosis, clearly dissociated from the signal of the nucleus pulposis in that it is surrounded superiorly, inferiorly, posteriorly and anteriorly by the low intensity (black) signal of the annulus fibrosis and is appreciably brighter than that of the nucleus pulposis" (Page 362).*[118]

This finding was identified on a midsagittal T2-weighted image; it may occur centrally in an otherwise normal annulus, in a bulging annulus, or be located superiorly or inferiorly behind the edge of the vertebral body in a severely bulging annulus. In a series of 500 consecutive patients, the per-patient prevalence was 29%; the per-disc prevalence of an HIZ was 6%. The majority of HIZs were present at the L4 and L5 disc levels, confirmed in later studies.

The relationship of the HIZ to pain production was evaluated in a subset of 41 patients selected for the presence of an HIZ on prediscography MR imaging.[118] Discography was performed with the requirement of a nonpainful control disc for a diagnosis of discogenic pain. Pain responses were tabulated both as "exact" reproduction of pain as well as "similar" pain. In all, 118 discs were tested in 41 patients; the per-disc prevalence of the HIZ was 34%, reflecting selection bias. In detecting exact pain, the HIZ had a sensitivity of 82% and specificity of 89%, a 70% PPV, and a positive likelihood ratio (+LR) of 7.3. When the discographic criteria were relaxed to exact or similar pain, the specificity rose



• **Figure 20.9** High intensity zone (HIZ). Middle-aged male has previously undergone L4–5 decompressive procedure, without discectomy, for back and leg pain. Axial back pain was unrelieved. **A,** Sagittal T2-weighted magnetic resonance image (MRI) shows loss of T2 signal in the L4 disc with an high intensity zone (HIZ) in the posterior annulus. **D,** Axial T2 MRI image at L4–5 interspace demonstrates the HIZ *(arrow)* in the posterior annulus. **E,** Axial-enhanced T1 MRI image showing enhancement in the HIZ, also demonstrated in the sagittal fat-saturated T1 image **(B)**. Sagittal postdiscogram computed tomography **(C)** demonstrates an annular fissure at L4–5 leading to HIZ. Pressurization of the L4–5 disc produced concordant axial pain at <20 pounds per square inch (PSI) above opening pressure. (From Maus TP, Aprill CN. Lumbar discogenic pain, provocation discography, and imaging correlates. *Radiol Clin North Am.* 2012;50:681–704.)

to 97% with a PPV of 95%; there were only two false-positive cases where a disc bearing an HIZ was nonpainful. The investigators postulated that the HIZ represents a complex grade 4 fissure where the nuclear material has been trapped within the lamellae of the annulus fibrosis and become inflamed, accounting for the T2 hyperintensity, brighter than that of the parent nucleus. They advanced the HIZ finding as pathognomonic of a symptomatic disc. The publication of these findings elicited considerable interest and many subsequent studies[114,119–128] attempting to verify or refute its conclusions. Bogduk compiled the results of 12 studies addressing the HIZ as a predictor of a positive discogram, revealing a pooled specificity of 88% (sensitivity 45%) and a likelihood ratio of 3.8 for this imaging finding.[115] A more recent retrospective analysis of nearly 2500 discs in patients who underwent discography showed that the presence of an HIZ had a PPV of 0.71.[129]

Disc contour abnormalities have been studied as predictors of positive discography, and although associations have been identified, there is considerable disparity among studies without a clear pattern.[120,121,129]

Quantitative/Functional Imaging

Conventional imaging techniques for assessment of the intervertebral disc and spinal pain are qualitative (not quantitative), unable to evaluate disc substructure, and unable to discriminate among early/subtle changes of disc degeneration. Although not in routine clinical use in most radiology practices, emerging advanced MRI techniques attempt to address these limitations. These include quantitating the degree of "degenerative" changes affecting the intervertebral disc, quantifying its biochemical composition,

discriminating among early degenerative changes, and identifying subtle changes in key pain generator phenotypes.[130] Such techniques include but are not limited to T2 mapping, T1 rho mapping, MR spectroscopy, and ultra-short time-to-echo (UTE) MRI.

T2 mapping (also known as T2 relaxometry) involves quantification of the content of water, proteoglycan, and collagen sequence breakdown. These different tissues can be objectively quantitated based on different relaxation times (T2 "values" or "times"), which is an intrinsic tissue property that reflects the disc's molecular environment.[131] These T2 relaxation times tend to decrease with age, and decreased T2 relaxation times correlate well with an increased grade of both disc and cartilaginous endplate degeneration.[132–135] Objective and continuous grading of disc generation may be possible by histogram analysis.[136] Some studies suggest that disc degeneration as quantified by T2 mapping may correlate with increasing low back pain, allowing differentiation of chronic low back pain patients from controls.[137] Others suggest that quantitative T2 mapping may be able to indicate discs at-risk for future herniation and correlate with patient's clinical status at longer term follow up.[138] One potential advantage of T2 mapping is the ability to indicate pathologic changes of the disc before it is evident subjectively to human readers. However, to date, normative values of T2 times are lacking, both within individual patients and across patient populations.[139] Thus T2 mapping is not yet able to supplant traditional visual assessment of MR images. Some data suggest that healthy discs in a given patient may provide the best definition of normal when available, to which abnormal levels could be compared.[139] There are many reasons why such quantitative imaging is not a panacea for the assessment of back pain. For instance, T2 calculations may be affected by unique subtle variations in the magnetic environment, such that different values may result from scan to scan, even when imaging equipment and scanning parameters are identical.[139] T2 times can also be affected by confounding variables such as specific lumbar levels among non-degenerated and degenerated discs,[140] time of the day,[141] and axial loading of the spine.[142] Precisely where to measure the quantitative features is an added complexity for quantitative imaging; for example, discs can be analyzed at the level of the anterior outer annulus, posterior outer annulus, or nucleus pulposus/inner annulus. The inherent limitation of not being to precisely delineate these different substructures further complicates matters.[139] In addition, the study methodology varies, including the use of either axial or sagittal imaging. Many publications in the quantitative imaging arena are also limited by relatively small sample sizes.

Meanwhile, mapping of the T1 rho time constant quantifies the degree of cartilaginous degeneration by assessing water molecule dispersion within the discal cartilage. T1 rho is an MRI relaxation time parameter that is sensitive to low frequency interactions between macromolecules and bulk water.[143] The dynamic range of T1 rho values is greater than that of T2 relaxation times.[131,143] Lower T1 rho values are found in degenerated discs and may correlate with discogenic pain.[144] In a high field strength (9.4 T) animal research, data from Paul and colleagues suggest that T1 rho mapping correlates better than T2 mapping with biochemical, histologic, and glycosaminoglycan characteristics of the disc.[143]

MR spectroscopy (MRS) can also evaluate the biochemical structure of tissues. After initial reports of the potential utility of this technique for assessing the intervertebral disc based on cadaveric and ex vivo data, in vivo studies began emerging. A recent study by Gornet and colleagues showed a correlation between discography results and MRS analysis of disc structure (proteoglycan and collagen) and acidity (lactate, alanine, propionate).[145] MRS showed the ability to discriminate discogram positive from negative discs and the potential for this information to affect surgical outcomes.[145] Some investigators have correlated multifidus muscle fatty atrophy with chronic low back pain and disc degeneration, with intramyocellular but not extramyocellular lipid accumulation as detected by MRS showing association.[146,147]

Quantitative imaging has also been applied to the cartilaginous endplate, such as with the use of UTE MRI. On conventional T2-weighted images, the endplate signal is hypointense and its integrity is difficult to assess.[130] UTE MRI results in the endplate as signaling hyperintense and affords the potential of assessing the morphology and biochemical structure of the endplate.[130] Quantitative measurements of endplate thickness on 3-dimensional UTE MRI appear to be associated with adjacent disc degeneration.[148] Some investigators have also used UTE MRI to assess the intervertebral disc. A hypo- or hyperintense band within the disc on UTE imaging may correlate well with disc degeneration, low back pain, and disability.[149]

In summary, quantitative high-resolution imaging techniques such as those described above show promise in evaluating degenerative findings involving the intervertebral disc. They offer the possibility of evaluating both structural and functional characteristics of the disc. The hope is that one or more such techniques could be implemented into routine or problem solving clinical practice to identify clinically meaningful and potentially actionable evidence of subtle/early disc degeneration.

Imaging Correlates: Conclusion

Imaging identification of discogenic pain is challenging for a variety of reasons. (1) There is no pathologic or surgical gold standard. (2) The existing standard of comparison, discography, is ultimately unproven, is subjective in its interpretation, and has evolved over time in its criteria for a positive test. None of the studies reviewed earlier use the most current and restrictive criteria, those of Spine Intervention Society (SIS). (3) The imaging findings likely have threshold effects, where only a significant expression of the finding (intensity of an HIZ, extent of marrow change) is a useful predictor of discogenic pain. Most studies do not account for this factor. (4) Imaging findings are likely technique dependent to an unknown degree, and imaging techniques are evolving.

The best available imaging predictors of discogenic pain, when applied to a select population of patients with axial back pain, in whom other pain generators have been excluded, are Modic endplate changes and the HIZ. Discography remains the reference standard for the diagnosis of discogenic pain. Quantitative imaging techniques have emerged and are evolving, but not in widespread clinical use.

Cervical Discogenic Pain: Imaging Correlates

This discussion has purposely focused on the lumbar spine. The lumbar spine segment is most commonly afflicted with discogenic pain, and the literature regarding its pathogenesis and evaluation with imaging and provocation discography, although challenging, is of greatest depth. The cervical intervertebral disc is structurally distinct from the lumbar disc. There is no posterior annulus, and the small nuclear compartment disappears early in life; the residual fibrocartilaginous plate normally develops fissures as mere age-related change.[101] There are no morphologic features at discography that contribute to a diagnosis of discogenic pain. Diagnosis

is reliant entirely on the provocation of concordant pain, with the requirement of nonpainful control discs.

As in the lumbar segment, structural age changes (loss of T2 signal, loss of disc space height, contour abnormality) are ubiquitous in cervical MRI studies. The Matsumoto study[33] cited earlier examined 2480 cervical discs in asymptomatic subjects and noted loss of T2 signal in 17% of males and 12% of females between ages 20–30, and 89% of males and 86% of females over 60 years old. A 10-year follow up of this study by Okada and colleagues demonstrated that progression of degenerative findings occurred in most patients (81%).[150] The only factor related to this progression was age. Clinical symptoms developed in a smaller proportion of subjects (34%). Daimon and colleagues then published a 20-year prospective longitudinal follow up of this study in 2018.[151] Progression of degenerative findings was essentially ubiquitous, seen in 95% of patients. The rate of progression of structural findings on MRI increased with age. Only the progression of foraminal stenosis had any association with the development of clinical symptoms (specifically, the onset of upper limb pain). In another study by Okada,[152] 89% of asymptomatic subjects (mean age 49 years) exhibited structural age changes on MRI; another group of patients (mean age 46 years) with symptomatic lumbar disc herniations but asymptomatic of neck pain showed cervical disc age-related change in 98% of the patients. There is a paucity of literature addressing the correlation of imaging findings with cervical discography. An early study by Parfenchuck (1994) showed only a modest ability of MRI findings of T2 signal loss or disc contour abnormality to predict a positive cervical discogram (sensitivity = 73%, specificity = 67%).[153] Schellhas' (1996) study suggested that MRI cannot reliably predict a positive cervical discogram.[154] A subsequent study by Zheng[155] again demonstrated only a modest predictive value of MRI using parameters of T2 signal loss and disc contour abnormality (sensitivity = 73%, specificity = 49%). The inflammatory disc parameters that proved to have such high specificity in the lumbar region are either unusual or little studied (Modic change) or have no anatomic existence (HIZ) in the cervical region. Occasionally foci of elevated T2 signal are observed in the posterior cervical disc, but in the absence of a posterior annulus, the anatomic correlate is unclear. Imaging identification of discogenic pain in the cervical spine remains elusive. Cervical discography remains the reference standard in the diagnosis of cervical discogenic pain. In patients with neck pain with or without neurologic symptoms, a study of 1059 patients revealed that the number of degenerated disc levels and the degree of cervical disc degeneration increases significantly with age.[156] C5–6 was the most common degenerated level, followed by C4–5 and C6–7. C5–6 and C6–7 were most common in those patients with two-level degeneration, followed by C4–5 and C5–6, and C3–4 and C-5. Degeneration was seen at contiguous levels, with skip level degeneration uncommon.

The imaging investigation of discogenic pain highlights a theme common to this chapter: physiologic parameters have greater significance in pain syndromes than purely structural alteration. To be ultimately valuable in the diagnosis of discogenic pain, imaging must move beyond macroscopic descriptions of morphology to the realm of biochemical imaging, quantifying the change in nuclear constituents over time. Besides characterizing biochemical nuclear matrix degradation, imaging will also need to identify inflammatory mediators in the disc and adjacent cartilaginous endplate more precisely. Perhaps then we will truly be capable of the noninvasive diagnosis of discogenic pain.

Vertebrogenic Pain

Recently, the so-called vertebrogenic model of pain has emerged as a potential alternative to the discogenic model. The vertebrogenic model is based on the hypothesis that nociceptors in the endplates can cause acute or chronic pain.[157] This theory, that low back pain may arise from the endplates rather than the disc, has been increasingly supported by a growing body of literature.[158,159]

At the root of the vertebrogenic model of pain is the concept that endplates are inherently prone to spondylotic changes. This is because of the conflicting functional roles held by endplates. Endplates must be strong enough to withstand the substantial physiologic stress put upon the spine. However, because discs lack a dedicated blood supply, endplates must also be porous enough to allow for passive transport from the vertebral body capillaries.[160] This porosity, in the setting of substantial tensile strains placed upon the vertebral bodies, frequently results in damage.[161] Some endplate regions are particularly susceptible to destructive changes, likely related to normal anatomic variations in endplate composition. For example, an endplate's center is thinner than its periphery, and superior endplates are thinner than their inferior counterparts.[162]

Once endplates are damaged, pro-inflammatory mediators can communicate between the disc and the vertebral body bone marrow.[159] This is typically followed by a cascade of spondylotic changes, in which cross-talk between the disc and bone marrow leads to progressively increasing inflammatory mediators.[163] Ultimately, such changes result in the degradation of endplates in regions often specific to the spinal level and location within the endplate.

On MRI, this spondylotic process typically appears as Modic changes. Modic changes, as discussed above, are associated with low back pain and are relatively specific imaging markers for predicting the reproduction of symptoms during provocative discography.[114] The association between Modic changes and provocative discography would seem to support the discogenic model. However, the closely related innervation between the annulus and endplates means that pain could be elicited from the endplate or disc. Some authors have opined that the correlation between MR findings and provocative discography presents some of the best evidence for the vertebrogenic model of low back pain.[161] Nevertheless, it remains impossible to distinguish between vertebrogenic and discogenic pain confidentially.

Anatomically, vertebrogenic pain is usually attributed to nociceptive innervation by branches of the basivertebral nerve (BVN). The BVN stems from the sinuvertebral nerve and enters the vertebral body via the posterior basivertebral foramen before branching along the endplates.[164, 165] The BVN has been shown to contain substance P, protein S-100, PGP 9.5, and calcitonin gene-related peptide, confirming its role in nociception.[163,166]

The innervation density of the vertebral body endplates is similar to the annulus and is greatest within the central endplate.[167] In healthy endplates, the innervation is modest in quantity.[167] However, damage to cartilage and subchondral bone induces proliferation of sensory nerve fibers, thought to be a chemotactic response to elements of disc breakdown.[111,168,169] Spondylotic changes may lead to a greater density of innervation by branches of the BVN, accounting for the localization of pain to the vertebral body endplates.

The vertebrogenic model has led to the recent development of novel therapeutic approaches to treat low pain back. Among these, BVN ablation using radiofrequency (RF) energy has gained the greatest interest.[170,171] Both single-arm studies[172,173] and randomized

control trials[170,171] have been completed. The results have overwhelmingly demonstrated the efficacy of BVN ablation. For example, Fischgrund et al. found that patients treated with intraosseous BVN ablation showed superior improvement in Oswestry Disability Index (ODI)—an outcome marker for patients with low back pain—and a greater rate of response compared to control patients treated with sham procedures.[170] Khalil et al. compared the efficacy of BVN RF ablation to standard care in patients with low back pain. The authors reported clear superiority of ODI-based outcome in the treatment group, with early statistical power resulting in termination of study enrollment and offering cross-over to the control group.[171] Laser ablation of the BVN, too, has been used with promising results.[174]

Despite the encouraging results demonstrated in these early trials, additional studies will have to determine the safety and long-term efficacy of BVN ablations. In addition, trials to date have been restricted to the lower spine (L3–S1), and patients with Modic I or II changes on MRI. Further investigation is needed to understand whether procedural success can be translated to other levels in the spinal column. Finally, it will be important to develop a reliable set of clinical, imaging, and/or testing (e.g. provocative discography) criteria by which vertebrogenic pain is diagnosed and whether such criteria can be used to differentiate vertebrogenic from discogenic pain.

Imaging of Axial Pain Generators

Zygapophysial Joint (Z-Joint, Facet Joint)

The supporting structure of the posterior column of the spine includes the paired facet joints with their associated capsules, the ligamentum flavum, the intraspinous and supraspinous ligaments joining the spinous processes, and the intertransverse ligaments. The inferior articular process of the facet joint faces anteriorly and is convex in configuration. On axial images, the inferior articular process is the more posterior component of the joint. The superior articular process (SAP) has a concave articular surface that faces posteriorly and medially. On axial images, it appears as the anterior component of the joint. In an erect standing position, the lumbar facet joints bear approximately 16% of the compressive load; they bear essentially no load in a flexed sitting position. With the loss of disc space height, the lumbar facet joints will bear proportionally more axial load. The fibrous joint capsule has been demonstrated to be richly innervated by nociceptors and proprioceptive fibers.[175] In a normal state, nociceptors such as those seen in the facet joint capsule have a high threshold and would not be expected to discharge unless loads are supraphysiologic. However, in the presence of pathologic joint inflammation, synovitis, chemical mediators may sensitize these nociceptors, and supraphysiologic levels of stress may no longer be required to stimulate pain. Such inflammatory mediators (substance P, bradykinin, phospholipase A2) have been detected in the facet joint capsule.[176]

There is thus a pathoanatomic basis for facet joint-mediated pain, particularly in the presence of facet synovitis. The imaging challenge in identifying a potentially painful joint lies in the well demonstrated specificity fault, that imaging changes of morphologic facet arthrosis (subchondral sclerosis, erosions, or cyst formation, osteophytes, joint space narrowing, vacuum phenomena) are age-related changes and do not correlate with pain. The reference standard for facet pain is positive comparative dual medial branch blocks, as there are no reliable physical exams or historical features allowing a confident diagnosis of Z-joint pain.[101] Schwarzer and colleagues semi-quantitatively scored CT finding of structural facet arthrosis and found no relationship to Z-joint pain as determined by placebo controlled medial branch blocks.[177] More recently, Cohen and associates showed no association between MRI findings of structural facet arthrosis and pain relief with dual medial branch blocks and subsequent radiofrequency rhizotomy.[178] These structural changes become universal by the sixth or seventh decade of life; they do not represent active inflammatory disease causal of pain.[179]

Instead, imaging must look to identify physiologic, not structural, markers of active facet synovitis. Imaging techniques that may be applicable include the technetium pyrophosphate bone scan (including its technologic evolution SPECT and SPECT/CT) and the MRI physiologic imaging parameters of T2 hyperintensity and gadolinium enhancement. Technetium pyrophosphate bone scans detect hyperemia and accelerated bone turnover, which may be considered manifestations of active inflammation. Dolan and associates[180] compared the response to intra-articular facet joint injection guided by clinical exam versus positive SPECT studies; there was a significantly greater short term (one- to three-month) clinical response in the SPECT-guided injections. A similar study by Holder and colleagues, using response to uncontrolled intra-articular injections as the reference standard, identified a 100% sensitivity and 71% specificity for SPECT scans in the detection of facet joint-mediated pain.[181] Pneumaticos and colleagues prospectively studied patients undergoing intra-articular injections in three groups: injections guided by positive SPECT scans, injections in patients with negative SPECT scan guided by clinical exam, and injections in patients without SPECT studies guided by clinical exam.[182] The patients whose injections were directed to SPECT-positive joints had significantly better clinical outcomes than the other two groups, as well as lower costs as fewer joints were injected. McDonald used SPECT/CT to identify joints for injection in 37 patients with clinical facet joint lumbar pain. The mean visual analog score dropped from 7.2–2.8, with an average duration of benefit of 2.2 months; only 1 in 37 patients did not report benefit. The fused SPECT/CT images were useful in distinguishing the L4–5 and L5–S1 facet joints.[183]

There is no correlation between the degree of morphologic facet arthrosis and the intensity of SPECT activity.[180] Rather, the phase of active synovitis correlating with pain production may occur relatively early in the progressive development of structural changes of facet arthrosis. Kim and colleagues correlated MRI findings in the facet joints with SPECT; they noted that the MRI appearance of T2 hyperintensity in the synovium, intrasynovial fluid, and cartilage disruption best correlated with a positive SPECT, here used as a reference standard for active facet synovitis.[184] More extensive structural manifestations of facet arthrosis did not demonstrate the physiologic finding of SPECT activity. Cervionke and colleagues have demonstrated an indirect association of T2 hyperintensity within and about the facet joint with axial pain.[185] T2 hyperintensity in the adjacent pedicle has also been associated with axial pain of facet origin; this finding can also be seen in pedicle or pars stress fractures. T2 hyperintensity accompanying facet synovitis may also be seen in the surrounding multifidus muscle, occasionally sufficiently extensive enough to raise concern of a sinister process. Gadolinium enhancement in and about the facet joint also suggests facet synovitis. Ultimately, the physiologic parameters of edema, hyperemia, and accelerated metabolic activity as detected by increased SPECT or SPECT/CT activity, and T2 hyperintensity and gadolinium enhancement on MRI must be evaluated as predictors of facet joint pain against the current reference standard, comparative medial branch blocks. Prevalence

studies of these parameters in populations asymptomatic of back pain are also needed for researchers to understand the specificity of these imaging observations. Despite the lack of absolute validation, if the patient is going to undergo an MRI for evaluation of axial pain, a fat-saturated or STIR sequence should be performed, as it represents the best chance of demonstrating physiologic findings (T2 hyperintensity), which may identify an axial pain generator (Fig. 20.10).

Various investigations have provided insight into the potential correlation of facetogenic pain with physiologic imaging findings of the facet joints. Lehman and colleagues retrospectively reviewed the utility of 212 SPECT/CT exams of the spine and sacrum over four years.[186] These exams were most commonly used in the diagnosis and management of pain, helping to identity pain generators and frequently resulting in a resultant change in clinical management. However, Lehman and his colleagues also studied 74 patients who underwent subsequent percutaneous facet joint steroid injection or comparative medial blanch blocks after a SPECT/CT scan.[187] Interestingly, the targeted facet joint treatment(s) was frequently discordant with the facet joint(s), demonstrating increased uptake on the nuclear medicine study. In approximately one-third of patients, the activity did not correlate with clinical findings. Similarly, when comparing facet joint activity on SPECT/CT with facet joint signal change on MRI with fat suppression, Lehman and colleagues found these two imaging findings did not always correlate and therefore should not be considered interchangeable.[188]

Besides SPECT/CT, other hybrid imaging modalities that are being used in at least the research setting to evaluate facet joint arthropathy are PET/CT and PET/MRI. PET/MRI is an alternative, emerging imaging modality that offers the possibility of evaluating facet joint inflammation with both radiotracer uptake and MRI findings of edema and/or enhancement. One of the elements for its appeal is the lack of ionizing radiation associated with the cross-sectional (MR) component, unlike the CT aspect of SPECT/CT and PET/CT. In a prospective study of 10 patients with clinically suspected facetogenic low back pain at specific levels, 18F-fluorodeoxyglucose (FDG) activity did show high concordance with MRI findings of considerable facet inflammation (prominent posterior element osseous or adjacent soft tissue edema/enhancement).[189] However, there was low concordance of both MRI findings of inflammation and FDG activity with the clinically implicated joints. Future research is needed to further elucidate the role of such hybrid imaging technologies, including ideally a comparison of imaging findings with the results of medial branch blocks.[190] One such prospective study by Freiermuth and colleagues included 29 patients; the sensitivity and specificity of SPECT/CT for a positive response after a medial branch block were 57% and 77%, respectively.[191] In addition to FDG-PET, some investigators are using sodium fluoride ([^{18}F]-NaF) PET (combined with either CT or MRI) to evaluate facet joint inflammation. This radiotracer can detect bone turnover. In one study of six patients with facetogenic low back pain who underwent [^{18}F]-NaF PET/MRI, a significant positive correlation was observed between maximum facet joint tracer uptake and clinical disability.[192] Such pilot data are promising but require further validation.

Space of Okada

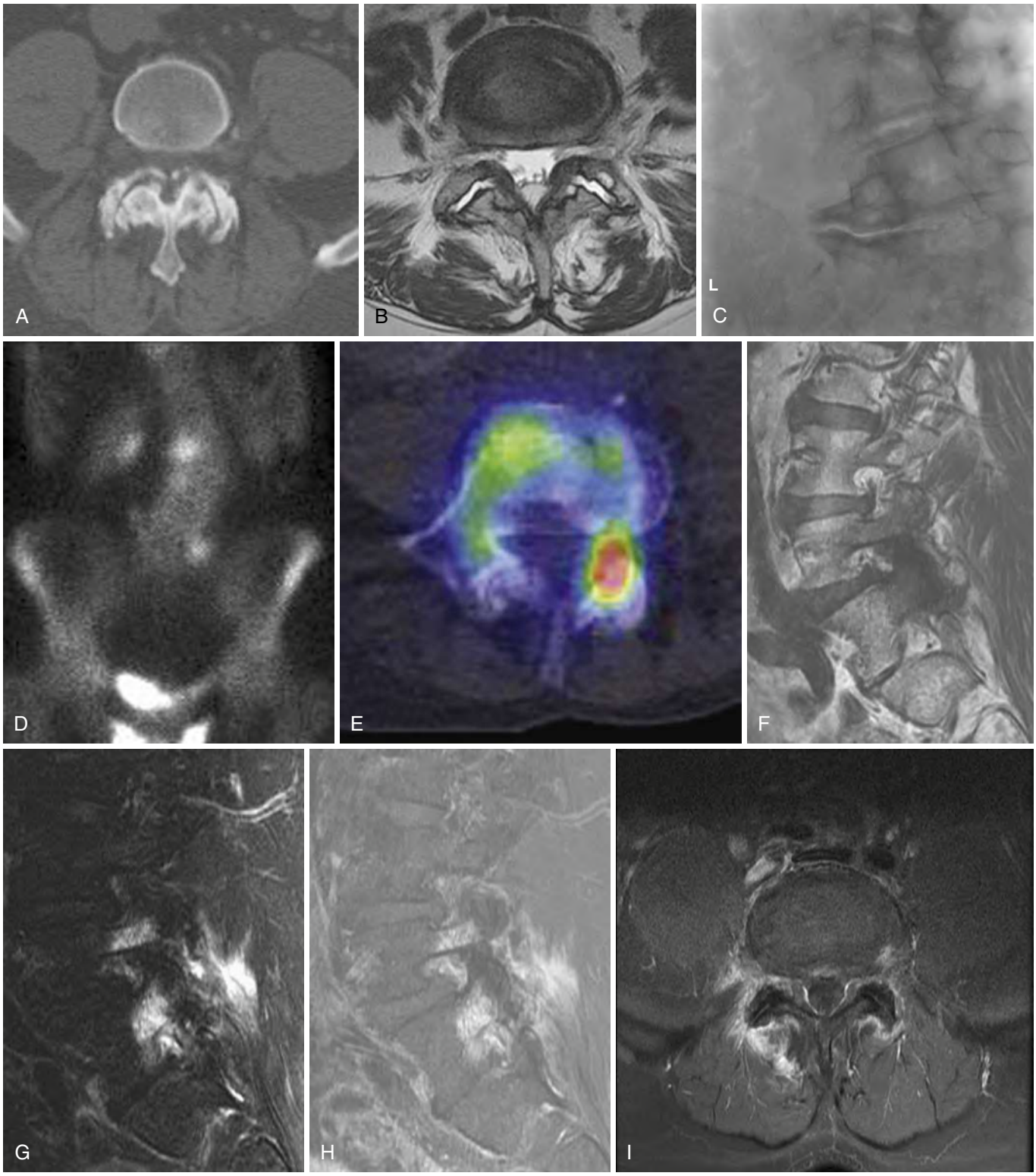
A tissue pathway between contralateral same segment facet joints was initially described in the cervical region by Dr. Kikuzo Okada in 1981; 80% of cervical facets demonstrated a communication between the joint capsules via a space situated dorsal to the ligamentum flavum in the axial plane and the interlaminar space in the coronal plane.[193] This communication is frequently observed in intra-articular injections of cervical facet joints that are structurally normal on imaging or exhibit only modest evidence of synovitis or structural arthrosis. In the lumbar region, this communicating pathway is commonly observed only in the face of advanced facet arthrosis; it may also be observed in the presence of defects in the pars interarticularis. This lumbar retroligamentous pathway also commonly communicates with an adventitial bursa within the interspinous ligament (i.e. Baastrup's disease).[194]

This pathway may serve as a means of transmission of infection or, more commonly, noninfectious inflammatory change between multiple joints and tissue compartments.[194] When the imaging findings of inflammation and/or fluid in the space of Okada are correlated with low back and/or radicular back pain, Lehman and colleagues in their pictorial review termed this clinical setting as the posterior ligamentous complex inflammatory syndrome.[195] In patients with lumbar axial pain and spondylolytic defects, this posterior element inflammatory complex may involve four facet joints, the bilateral pars defects, and the interspinous ligament. It may have a capacity of 4–6 cc of fluid in the author's experience. It is also a potential confounding space in epidural steroid injections. For example, this space may provide a false loss of resistance superficial to the dorsal epidural space during interlaminar injections; contrast injection may subsequently fill either facet joint at that segment level or the interspinous ligament (Fig. 20.11).[196] Similarly, during cervical and lumber transforaminal epidural steroid injections, in which the needle tip may be at least partially in or near the facet joint capsule, contrast injection will occasionally demonstrate flow from the ipsilateral facet joint to the space of Okada, simulating dorsal epidural flow.

Sacroiliac Joint

The sacroiliac joint is a large irregular synovial joint lined by thick hyaline cartilage on its sacral surface and thinner fibrocartilage on its iliac surface. The inferior and anterosuperior aspects of the radiographically perceived joint are synovial; its superior and posterior aspect is ligamentous. The posterior surface of the joint is covered by thick interosseous and dorsal sacroiliac ligaments. There is minimal movement of the joint, except under the hormonal influences of pregnancy. However, this modest mobility is vital for appropriate gait. The synovial portion of the joint is uniformly present in young adults, with a cartilage thickness of 2–5 mm; the synovial space may be attenuated in older adults by fibrous adhesions, but fusion across the joint is not a normal change of aging. Potential communications between the synovial space and the dorsal sacral foramina, the L5 epiradicular sheath, and the ventrally situated lumbosacral plexus have been observed.[197] These could explain radicular pain associated with sacroiliac joint dysfunction, as well as occasional lumbosacral temporary motor block after sacroiliac joint intra-articular injections, related to the spread of anesthetic. Although the surface area of the joint is large, its synovial space is of small volume, ranging from 1–2.5 cc.[198,199] Innervation of the sacroiliac joint is complex and remains controversial. Consensus suggests a dominant dorsal innervation from the L5 and S1–S4 dorsal rami.

Osteoarthrosis of the sacroiliac joints may be seen in pathologic specimens of young adults, but it is not generally appreciable radiographically until middle age. Changes in cartilage degeneration are more prominent on the iliac side of the joint. Beyond 40 years of age, many subjects have detectable narrowing of the

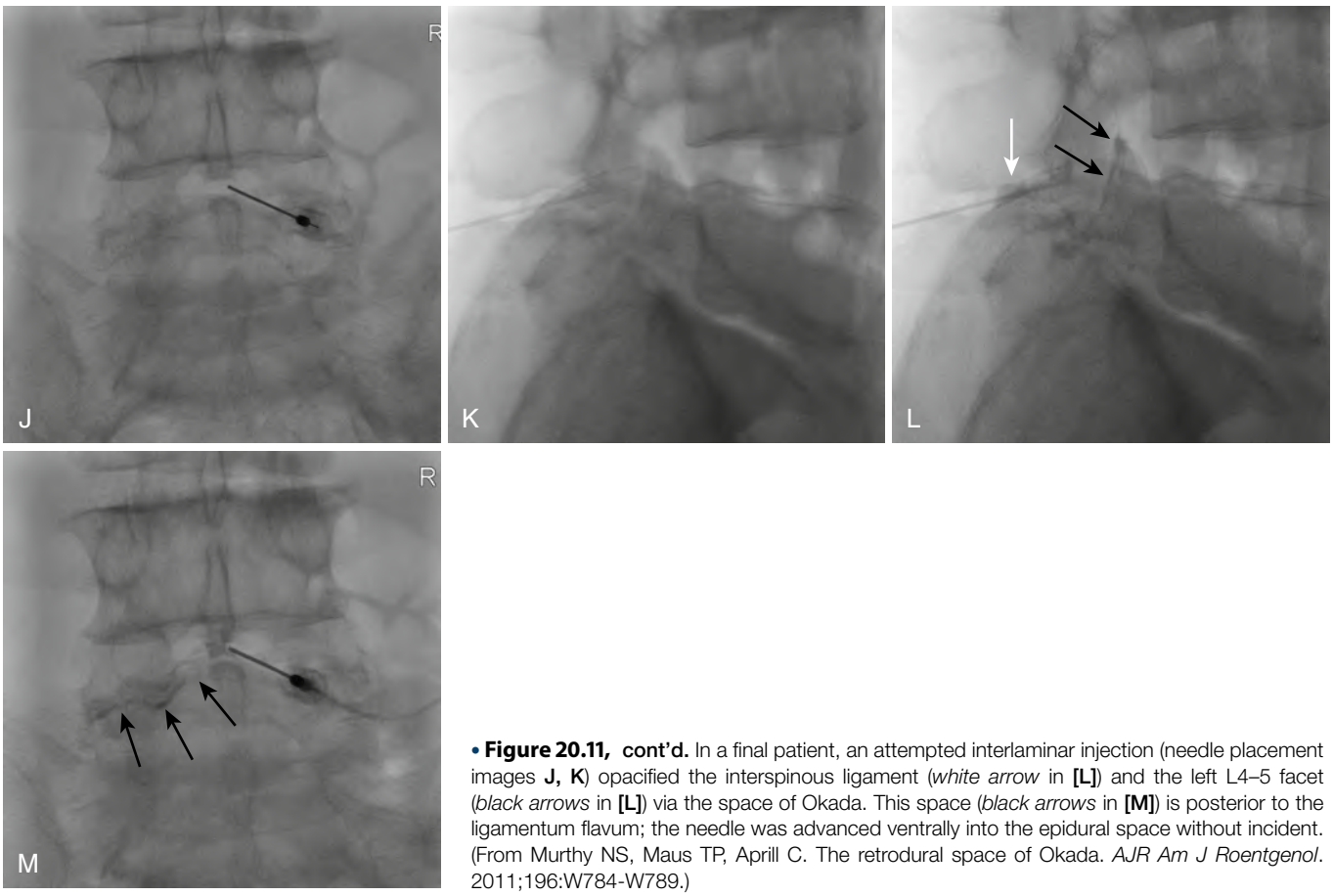


• **Figure 20.10** Imaging of facet arthrosis and synovitis. The changes of arthrosis (i.e. joint space narrowing, osteophytes, subchondral cysts, or sclerosis) as seen in the CT image **(A)**, the T2 MRI image **(B)**, or the radiographic image **(C)** do not correlate with pain. Planar bone scan image **(D)** of the same patient as **(C)** shows increased uptake near the lumbosacral junction on the left in this patient with left-sided axial pain. SPECT/CT image **(E)** provides better anatomic localization to the left L4–5 facet. In another patient with right-sided axial lumbar pain, T1 MRI image **(F)** shows a low signal in the right L5 pedicle and the right L4–5 facet. Fat-saturated T2 sagittal image **(G)** demonstrates T2 hyperintensity in L4 and L5 pedicles, L4–5 facet, and adjacent soft tissues. Enhanced T1 sagittal **(H)** and axial **(I)** images also demonstrate the extensive inflammatory response in this patient with active synovitis. T2 hyperintensity or enhancement in pedicles can occur in facet synovitis or stress fractures of the pars or pedicle. *CT*, Computed tomography; *MRI*, magnetic resonance image; *SPECT*, single-photon emission computed tomography.

sacroiliac joint, especially in its inferior portion. This may be accompanied by subchondral sclerosis and osteophyte formation, most prominent anteriorly and inferiorly. A vacuum phenomenon may be seen. As in the facet joint, changes of osteoarthrosis are a normal aging phenomenon and are not predictive of pain.

Evaluation of imaging features predictive of sacroiliac joint pain is yet again confounded by the lack of a pathoanatomic gold standard. Medical history and physical exam provocative maneuvers cannot consistently identify painful sacroiliac (SI) joints.[200] The reference standard for sacroiliac joint pain is the relief of

• **Figure 20.11** The space of Okada. Frontal fluoroscopic image **(A)** demonstrates the space of Okada providing communication between the bilateral C6–7 facets via the right-sided injection. In another patient **(B),** an attempted right L4 transforaminal injection opacified the superior recess of the L4–5 facet, traversed an L5 pars defect *(white arrow)* to the right L5–S1 facet, and opacified the space of Okada to a left L5 pars defect *(black arrow)* and the left L4 and L5 facets. Subsequent computed tomography **(C, D, E, F)** confirms the opacification of all these structures. The space of Okada is marked by the *white arrows* in **(D)**. The space of Okada may contain a small amount of fluid, which appears as T2 hyperintensity (*white arrows,* **G, H, I**). Note continuity with interspinous ligament (*arrow* in **[H]** and **[I]**).



• **Figure 20.11, cont'd.** In a final patient, an attempted interlaminar injection (needle placement images **J, K**) opacified the interspinous ligament (*white arrow* in **[L]**) and the left L4–5 facet (*black arrows* in **[L]**) via the space of Okada. This space (*black arrows* in **[M]**) is posterior to the ligamentum flavum; the needle was advanced ventrally into the epidural space without incident. (From Murthy NS, Maus TP, Aprill C. The retrodural space of Okada. *AJR Am J Roentgenol*. 2011;196:W784-W789.)

index pain with an intra-articular anesthetic block. This should ideally be either placebo controlled or a comparative block paradigm. Potential leakage from the joint capsule may complicate diagnostic specificity. Schwarzer[201] studied patients with chronic low back pain experienced below the lumbosacral junction. Using response to single blocks as the diagnostic criteria for sacroiliac pain yielded a prevalence of 30%. Requiring a positive block and a ventral capsular tear on postarthrographic CT yielded a prevalence of 21%; adding pain provocation with joint distension to the criteria lowered prevalence to 16%. The Maigne study using double blocks suggested a prevalence of 18.5%.[202] Subsequent work by DePalma[96] identified a prevalence of 18%; sacroiliac joint pain increased in prevalence with age up to approximately 70 years.

Structural changes of osteoarthrosis in the sacroiliac joint are poor predictors of pain. Elgafy and colleagues[203] scored CT features of arthrosis in SI joints and noted a sensitivity of 58% and a specificity of 69%. Physiologic imaging parameters suggesting the presence of hypervascularity, edema, or inflammation are more likely to predict pain. In the studies by Maigne[204] and Slipman,[205] technetium bone scans achieved specificities of 89.5% and 100%, although with low sensitivity, for sacroiliac pain as referenced by uncontrolled intra-articular injections. The MRI physiologic parameters of T2 hyperintensity and gadolinium enhancement have been studied primarily in the context of inflammatory spondyloarthropathies. MRI evidence of active inflammation (sacroiliitis) is intrinsic to the diagnoses of spondyloarthropathies and correlates well with clinical disease activity and therapeutic response to disease modifying agents (TNFα inhibitors) (Box 20.3).

Baastrup's Disease

Baastrup's disease, the apposition of the lumbar spinous processes resulting from hyperlordosis, segmental instability, or loss of disc space height, may degrade the interspinous ligament with the

• Box 20.3 Zygapophysial (Facet) and Sacroiliac Joint Pain

- Structural arthrosis, as seen by radiographs, computed tomography (CT) or magnetic resonance image does not predict pain.
- Physiologic parameters of hyperemia, edema, and increased metabolic activity may predict pain.
- These physiologic parameters may be assessed by T2 hyperintensity (STIR or fat-saturated T2 images), gadolinium enhancement, or increased uptake on single-photon emission computed tomography (SPECT) or SPECT/CT.
- There are no validation studies of physiologic parameters against accepted reference standards (dual, comparative blocks).
- There are no studies addressing specificity—that is, the prevalence of these findings in asymptomatic subjects.

formation of a pseudarthrosis or pseudobursa.[206] This may be a cause of focal midline lumbar pain. Such pseudobursa may have a synovial membrane and can communicate with facet joints or pars defects via the retroligamentous space of Okada.[193] The pseudobursa may extend anteriorly through a midline cleft in the ligamentum flavum and present on MRI or CT as a midline posterior epidural cyst, causing neural compression and contributing to radicular or claudicatory pain. It may be mistaken for a synovial cyst of facet origin but is distinguished by its posterior midline location, the relative absence of facet degeneration, and inflammatory change in the interspinous ligament.

Baastrup's disease may be identified on radiographs as contact between adjacent spinous processes with sclerosis, flattening, and enlargement. Not surprisingly, this structural change is commonly observed in asymptomatic individuals. In one study, it was present in 81% of individuals greater than 80 years old.[207] The authors also noted that "Baastrup's phenomenon" was observed in 41% of patients undergoing CT imaging for non-low back pain indications.[207] MRI findings of edema, inflammation (T2 hyperintensity, gadolinium enhancement), or a cystic fluid collection in the interspinous ligament are more likely to represent symptomatic disease, although this has not been well validated against anesthetic blocks. DePalma's study suggested that Baastrup's disease accounted for approximately 2% of axial low back pain.[96] In an MRI study by Maes and associates, imaging evidence of Baastrup's disease was present in 8.2% of subjects, most commonly at the L4–5 segment; nearly half of the patients had multiple-level involvement.[208] Baastrup's disease may also be identified as hyperemia and increased metabolic activity on technetium pyrophosphate SPECT or SPECT/CT studies as well as Fluorodeoxyglucose (FDG)-PET/CT scans. Focal uptake in the spinous processes is most likely to be inflammatory and should not be misinterpreted as metastatic disease. The distinction should be obvious when correlated with the simultaneously obtained CT images, which will show typical structural changes of arthrosis (Fig. 20.12).

Bertolotti's Syndrome

Bertolotti's syndrome describes the controversial association of transitional lumbosacral segments with mechanical back pain. It does not imply a specific mechanism of pain production. As discussed above, transitional anatomy is relatively common. In a large study of 4000 patients, Tini found no correlation between the presence of a transitional segment and low back pain.[209] The disc at the level of the transitional segment is often rudimentary, with little nuclear material; disc herniations seldom occur at this level.[89] Rather, stresses may be accentuated at the supra-adjacent disc level, where accelerated disc degeneration and an increased incidence of disc herniations have been reported (Fig. 20.12).

Axial low back pain in the presence of an asymmetric transitional segment has also been attributed to abnormal unbalanced motion at this level, with the neoarticulation of the transverse process with the sacral ala or the contralateral facet as the specific pain generator. Jönsson reported 11 cases of mechanical pain attributed to the neoarticulation despite normal bone scans.[210] Nine of 11 patients obtained pain relief with local anesthetic injection in the neoarticulation; a similar proportion of patients had improvement in pain with resection of the neoarticulation.[210] Physiologic imaging parameters (MRI T2 fat-saturated or STIR images, SPECT/CT) are more likely to be useful than structural changes, although no systematic studies have been performed. Brault reported a case of an adolescent athlete with focal mechanical pain consistently relieved by intra-articular injection of the facet contralateral to the neoarticulation. Interestingly, the bone scan showed increased uptake at the neoarticulation but not at the contralateral facet. Surgical resection of the neoarticulation resulted in complete relief of the contralateral pain at one year.[211] This may represent a case of pain generated by excessive facet capsular stresses caused by the asymmetric motion at this level, without detectable facet synovitis.

Transitional lumbosacral segments may thus be associated with axial pain, related to a neoarticulation, the contralateral facet at the level of an asymmetric neoarticulation, or IDD in the at-risk disc above a transitional segment. Radicular pain may be caused by a herniation in the adjacent segment disc or an extraforaminal entrapment at a neoarticulation. The presence of a transitional segment should always prompt meticulous attention to segmental enumeration because of both its intrinsic capacity for confusion and the seven-fold increased likelihood of an anomalous number of mobile presacral segments.[89]

Coccydynia

The radiographic evaluation of the sacrococcygeal region in patients with coccydynia remains controversial. This largely female pain syndrome is probably multifactorial in origin with contributions by somatic and neuropathic pain.[212] A single lateral view of the coccyx to evaluate for destructive osseous lesions is a reasonable screening study. Maigne has described a dynamic radiographic study to more fully evaluate the mobility of the coccyx.[213] This consists of a lateral radiograph with the patient standing for 10 minutes to visualize the coccyx without load, followed by a sitting lateral view, with the patient altering the pelvic position to that which stimulates the usual pain. Maigne and colleagues have studied coccygeal mobility and suggested that a normal coccyx may undergo from 5–25 degrees of angulation in moving from a standing to a sitting position. Flexion of the coccyx by more than 25 degrees with sitting as well as posterior subluxation of the coccyx with sitting and reduction with standing are considered pathologic and may be the anatomic basis of coccydynia.[213] Aggressive treatment decisions based on this evaluation are controversial. Advanced imaging has little role in this setting unless there is clinical suspicion of underlying systemic disease.

Pseudarthrosis, Postoperative Axial Pain

Patients with posterior fusion instrumentation may develop pain related to pseudarthrosis, infection, implant fracture or loosening, or the interface between the metal and the overlying soft tissue. Radiographs should be scrutinized for the integrity of the implant construct, loosening of pedicle screws (which will manifest as a halo of lucency surrounding the screws), or imaging evidence of pseudarthrosis. Anesthetic injection about prominent hardware may be useful in identifying this as a pain generator.

Despite advances in surgical technique and fixation hardware, fusion remains an imperfect procedure. Pseudarthrosis is defined as the failure to achieve a solid osseous fusion one year after attempted surgical fusion. It is manifested as persistent motion at the segment and absence of osseous trabeculae bridging the vertebrae. Approximately 15% of lumbar spinal fusions

• **Figure 20.12** Baastrup's disease and Bertolotti's syndrome as posterior element pain generators. An elderly male presents with neurogenic intermittent claudication. T2 fat-saturated sagittal image **(A)** and axial T2 image at the L4–5 interspace **(B)** demonstrate that the compressive lesion is a right paramedian dorsal cyst in continuity with the interspinous pseudobursae of Baastrup's disease. There are also facet joint effusions. In another patient with axial pain **(C),** a fat-saturated, enhanced T1-weighted image shows inflammatory enhancement in the interspinous ligaments of T12–L4. Sagittal T2 **(D)** and T1 **(E)** images of another patient demonstrate a large complex midline dorsal cyst emerging from an interspinous pseudobursae at the L3–4 interspace (axial T2 image **[F]**). A 17-year-old female (frontal lumbar spine radiograph **[G]**) presented with intractable left lumbosacral junction region pain. Note left pseudoarticulation (Bertolotti's syndrome). Single-photo emission computed tomography/computed tomography image **(H)** shows markedly increased uptake at the pseudoarticulation. Pain was relieved with injection into this site (fluoro image **[I]**; note that the patient is prone).

result in pseudarthrosis; the range of successful reported technical and clinical outcomes spans 16%–95%.[214] Rates of pseudarthrosis increased with the increasing number of fused levels and with risk factors including prior surgery, instability, deficient bone graft quality and quantity, and nicotine use (Fig. 20.13).

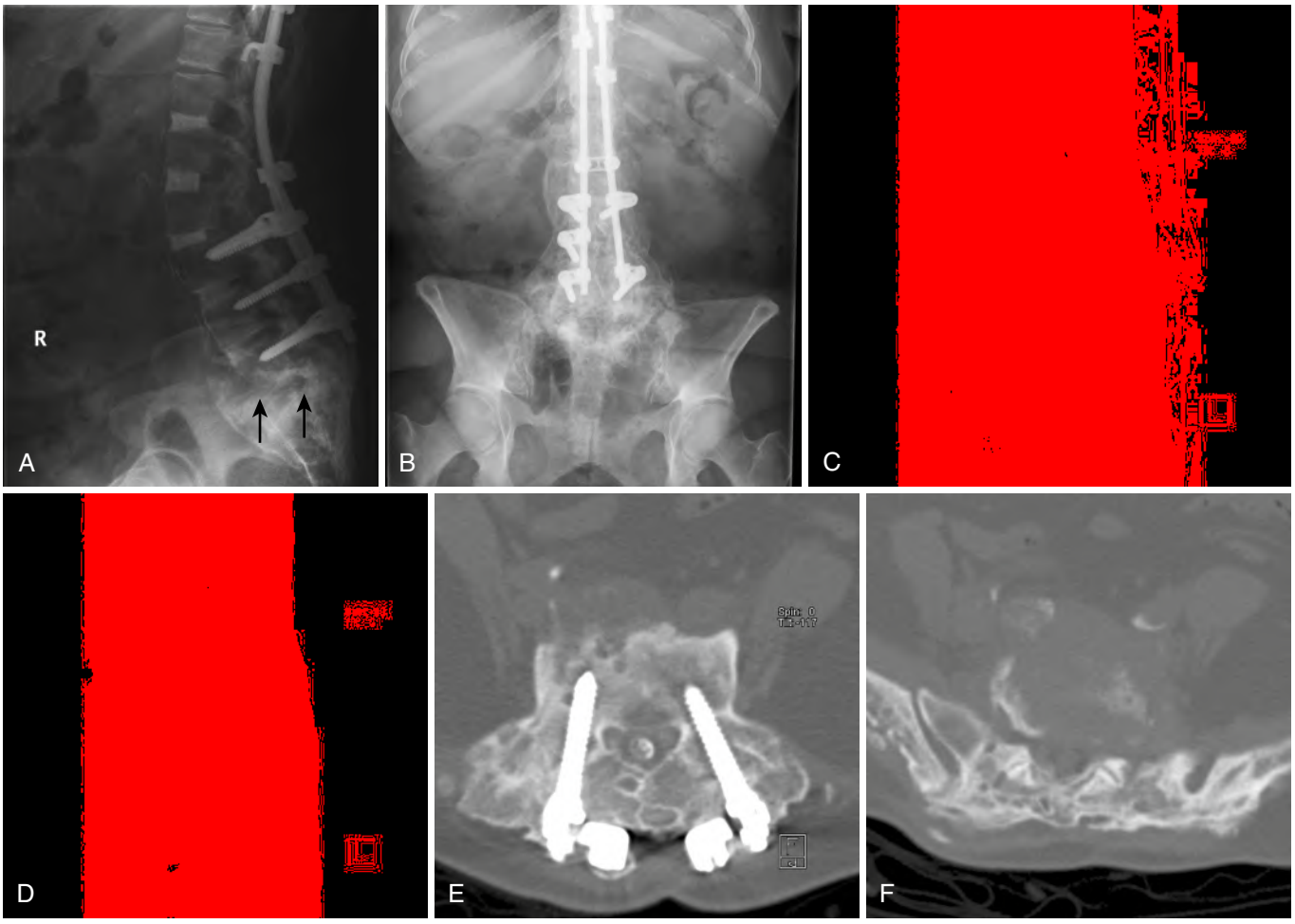
Detection of pseudarthrosis with imaging is of significance, as it is a cause of persistent or recurrent pain following surgery. The correlation is not exact; patients with radiographic pseudarthrosis may be pain free, and patients with solid fusions by all imaging techniques may have persistent pain arising from other factors. Therefore the clinical questions are two-fold: Is a pseudarthrosis present, and, if so, is it the cause of persistent or recurrent pain? The ultimate gold standard for fusion is surgical exploration; even this is not foolproof, as patients who have had hardware removal after intraoperative evaluation of stability have subsequently gone on to develop progressive deformity.[215]

Weight bearing radiographs are the primary tool in assessing stability and adequate fusion. In this setting, flexion-extension views likely add value. Radiographic evidence of instability includes the translation of 3 mm or more at L1–L4 or 5 mm at L5–S1. Radiographic fusion may take six to nine months, with ongoing remodeling for up to two years. The criteria for a radiographic solid interbody fusion are as follows:[216]

- No motion or less than three degrees of intersegment position change on lateral flexion and extension views
- Lack of a lucent area around the implant
- Minimal loss of disc height
- No fracture of the implant, bone graft, or vertebrae
- No sclerotic change in the bone graft or adjacent vertebrae
- Visible osseous formation in or around the cage

CT will provide greater sensitivity in the detection of pseudarthrosis, which manifests as lucent fracture lines with adjacent sclerosis or fragmentation of the bone graft, and fracture or lucency about implants. Ideally, to verify solid fusion, one wants to confirm the presence of continuous osseous trabeculae across the site of fusion. In patients with intervertebral cage devices, osseous trabeculae should be seen bridging the interspace through the cage and external to the cage.

Technetium bone scans with SPECT may be helpful. The fusion mass will be metabolically active for a prolonged period after surgery, and increased tracer uptake diffusely in the fusion mass is expected for several months. In normal healing, studies with serial



• **Figure 20.13** Pseudarthrosis on computed tomography (CT) myelography. This 71-year-old female is post multiple spine surgeries and has an instrumented fusion from the upper thoracic region to L5. She presents with bilateral leg pain in an L5 radicular distribution. Radiographs **(A, B)** show lucency with surrounding sclerosis at the L5 level. CT myelography sagittal reconstructions **(C, D)** reveal a pseudarthrosis at L5–S1 with Charcot or infectious features. Cultures were negative. Despite the instrumentation, the thecal sac is well demonstrated; it is patent at the L5 vertebral level **(E)** but obliterated at the L5–S1 disc level **(F)**. (From Thakkar RS, Malloy JP, Thakkar SC, et al. Imaging the postoperative spine. *Radiol Clin North Am.* 2012;50:731–747.)

bone scans have shown a steady decrease in tracer uptake after three months, with only minimal increased uptake at one year.[217] Increased uptake within the fusion mass beyond one year after surgery, or new increased uptake not present in prior studies, should raise concern for pseudarthrosis. On MRI, a solid bone graft should exhibit signal characteristics of normal marrow. Focal zones of T1 hypointensity, T2 hyperintensity, and gadolinium enhancement may indicate a site of pseudarthrosis with ongoing motion and inflammation. This requires careful inspection.

With disc arthroplasty, postoperative evaluation can occur by radiography or CT; radiography is more conservative of cost and radiation for serial follow up. The implant should be centered between the pedicles on AP images without penetration of the endplates. On lateral or sagittal images, the center of rotation should be in the posterior half of the disc space, but the implant should not extend beyond the posterior vertebral line.

The clinician and imager must also be aware of symptomatic adjacent segment disease as a cause of recurrent pain in the postfusion patient. Although controversial, this likely occurs at a rate of approximately 3% per year following lumbar fusion.[218] A similar rate has been associated with cervical fusion. The imaging findings will be those of discogenic pain. Radiographic evidence of adjacent segment disease may or may not be clinically symptomatic.

Pseudarthrosis and adjacent segment disease are two primary causes of pain in the postoperative patient, sometimes labeled the "failed back." Although conventionally considered a dread diagnosis, studies have shown that careful clinical evaluation, augmented by high quality imaging and provocation and anesthetic interventions, can identify the specific cause of pain in most cases. Waguespack and Slipman have each published reports on large series of patients with so-called failed back syndrome.[219,220] A specific diagnosis identifying the pain generator was achieved in over 90% of patients in both of these series. The most common diagnoses were foraminal stenosis (>20%), discogenic pain (20%), pseudarthroses (14%), neuropathic pain (10%), and recurrent disc herniation (7% to 12%), with lesser contributions from facet and SI joints. Each of these morphologic lesions has been individually addressed in the preceding sections. The imaging challenge is to systematically evaluate each segmental level for these potential pain generators despite the confusion of the surgically altered anatomy.

Imaging of Radicular Pain, Radiculopathy, and Myelopathy

Disc Herniation

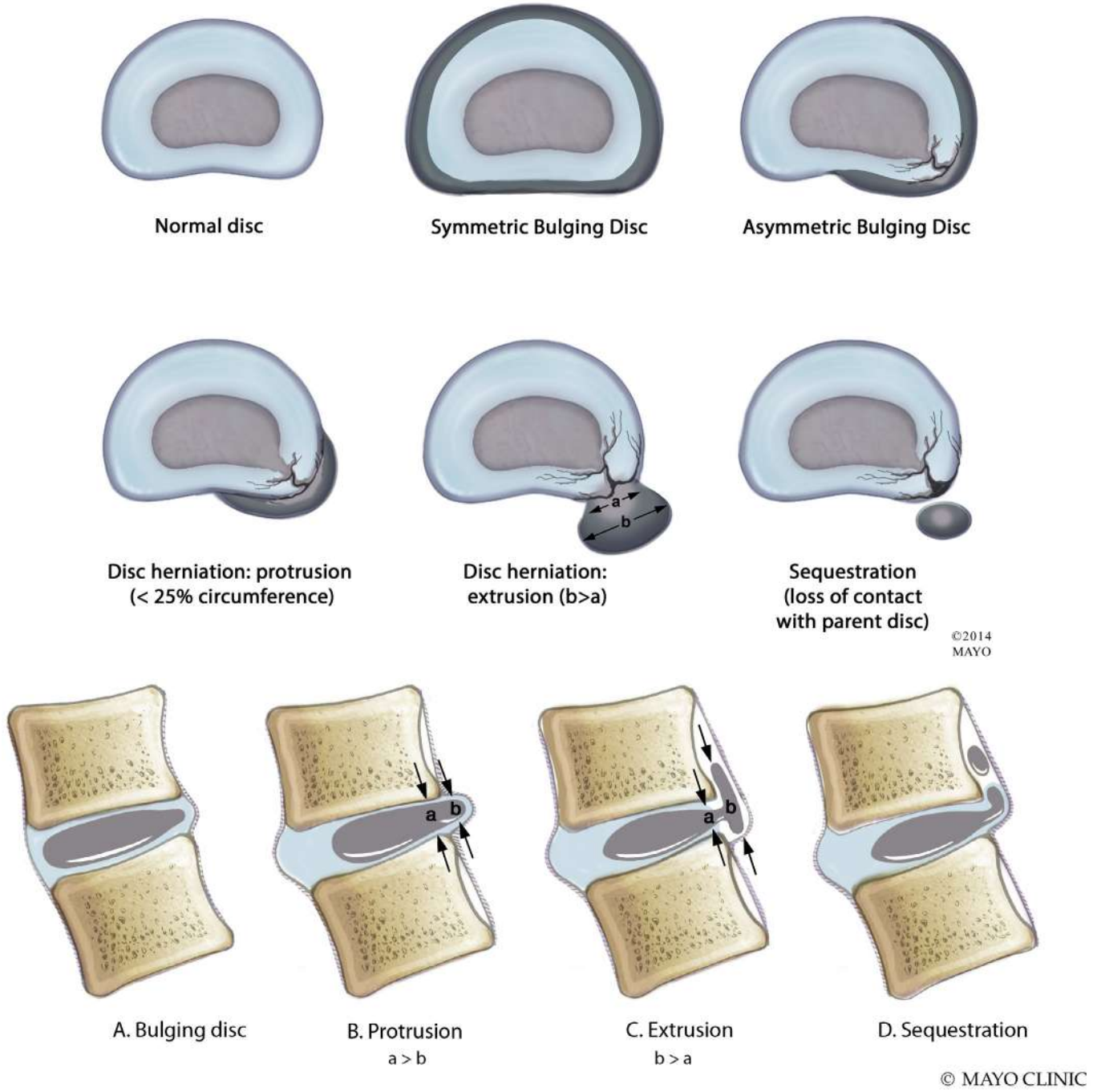
Radicular pain, or radiculopathy or myelopathy, has as its substrate neural compression and inflammation. Degradation of the nuclear matrix of the disc may occur in response to a variety of insults, including endplate infraction, genetically determined apoptotic chondrocyte cell death, diabetes mellitus, ochronosis, smoking, or infection. The nuclear compartment of the disc can no longer bear axial load, shifting its burden to the posterior annulus, which may undergo structural failure in the form of radial fissures, the anatomic basis of IDD. Besides potentially causing axial pain, these fissures may allow herniation of nuclear material into the outer annular lamellae as a contained protrusion or breach the annulus and pass into the epidural space as an extrusion. The mechanical compression of neural tissue and an induced inflammatory response conspire to provoke radicular pain or radiculopathy.

Mixter and Barr initially described the disc herniation as the cause of sciatica in 1934[221]; this observation, and the ability to relieve pain and neurologic dysfunction by surgical extirpation of the offending herniation, provided the basis for the first 70+ years of spine imaging. Myelography, CT, CT/myelography, and MRI were deemed useful in the patient with radicular pain or radiculopathy in the ability to first indirectly and later directly visualize the disc herniation and neural compression. The pathogenesis of radicular pain or radiculopathy is more complex than the simple compression of neural elements; an inflammatory response is also necessary to produce pain. The evidence supporting an inflammatory component in radicular pain was summarized by Mulleman and colleagues.[222,223] Neural compression in isolation produces nerve dysfunction, but not pain; exposure of compressed neural elements to the inflammatory response induced by disc nucleus pulposis results in radicular pain. This inflammatory response is mediated by phospholipase A2, interleukins 1 and 6, TNFα, and nitric oxide. The necessity of an induced inflammatory response for pain production provides a measure of understanding for the glaring specificity fault of disc herniation imaging: large disc herniations are often asymptomatic, and the severity of symptoms bears no relationship to herniation size.

The imaging description of disc herniations has historically been chaotic, with significant disparities among medical specialties and regions. Clarity was restored by a lexicon of lumbar spine nomenclature produced as a cooperative venture between multiple spine societies in 2001[224] and updated in 2014.[225] In this construct, spondylosis deformans describes those changes as thought to be because of normal aging. Degradation of the nuclear matrix may occur without structural failure of the annulus. Hence, there is relative preservation of disc space height and normal cartilaginous endplate and subchondral marrow. Anterior and lateral osteophytes are observed. MRI imaging shows loss of the normal intranuclear cleft and mild to moderately diminished T2 signal within the disc. Small concentric and transverse annular fissures may be seen in spondylosis; radial fissures are not considered a normal aging phenomenon. Small amounts of gas may be present within the disc that may be detected on plain films.

In this lexicon, pathologic discovertebral change is termed intervertebral osteochondrosis. This includes the changes of IDD, radial, and large circumferential fissures extending to the outer annulus. They may be accompanied by the development of posterior osteophytes that encroach on the central spinal canal. Besides posterior osteophytes, plain film manifestations of intervertebral osteochondrosis include large amounts of gas within the interspace, loss of disc space height, and endplate irregularity. On T2-weighted MRI images, the disc is of markedly diminished signal intensity. Disc herniations are common. Endplate cartilage erosion and reactive vertebral body marrow changes may also be present.[224]

Generalized disc displacement of over 25% of the circumference of the disc is a bulging disc. This can occur symmetrically throughout the circumference of the disc (symmetric bulging disc) or asymmetrically greater than 25% of the circumference of the disc (asymmetric bulging disc). The inclusive term for a localized or focal displacement of disc material is "herniation," which is defined as involving less than 25% (90°) of the disc circumference as viewed in the axial plane. Disc herniations can be either protrusions or extrusions, with the distinction between these two being one of shape (Fig. 20.14). In a protrusion, the width of displaced disc material in any plane does not exceed the width of its base at the outer margin of the disc space of origin. In an extrusion, the width of the displaced



• **Figure 20.14** Disc herniation definitions. Disc herniation definitions are depicted in the axial **(A)** and sagittal **(B)** planes. Note that the normal L1–L4 discs, shown here, are not round but an oblate structure whose dorsal margin is convex anteriorly. The L5 disc is normally oval in configuration, convex posteriorly. The definitions are elaborated in the accompanying text.

disc material exceeds its base in at least one plane. The presence of an extrusion shape suggests complete disruption of the outer annulus, and disc material has entered the epidural space. "Sequestration" is the term for loss of continuity of a disc extrusion with the parent disc from which it arose. Displacement of disc material away from the parent disc is termed "migration." Migration can occur caudally or cranially. A herniated disc can further be classified as contained or uncontained. A contained disc herniation is one in which the outer annulus fibrosis and/or the posterior longitudinal ligament is intact, whereas an uncontained herniation is one in which any such covering is absent. The shape definitions of protrusion and extrusion speak to this, but only by implication, not direct observation. While smooth posterior margins of disc protrusions on CT or MRI suggest containment and irregular margins suggest an uncontained herniation, CT or MRI can only rarely directly establish containment; post-CT discography can make this distinction.

Description of displaced disc material (Fig. 20.15) in the axial plane is defined by zones: the central canal zone defined by the medial margins of the facets (including the central and right/left central zones), the subarticular zone extending from the medial facet margin to the medial pedicle margin, the foraminal zone extending from the medial to lateral margins of the pedicle, and the extraforaminal (or far lateral) zone peripheral to the lateral pedicle margin. Therefore a right-sided disc herniation may be described as right central, right subarticular, right foraminal, or right extraforaminal. Similarly, the location in the sagittal plane (superior-inferior) is defined by levels in relationship to the vertebral endplate and pedicle margins. Extending from superior to inferior, the designations include the disc level, suprapedicular level, pedicle level, infrapedicular level, and the subsequent disc level. Although an element of subjectivity remains inherent in any usable system of terminology, careful adherence to these descriptors should allow a more coherent discussion of disc pathology.

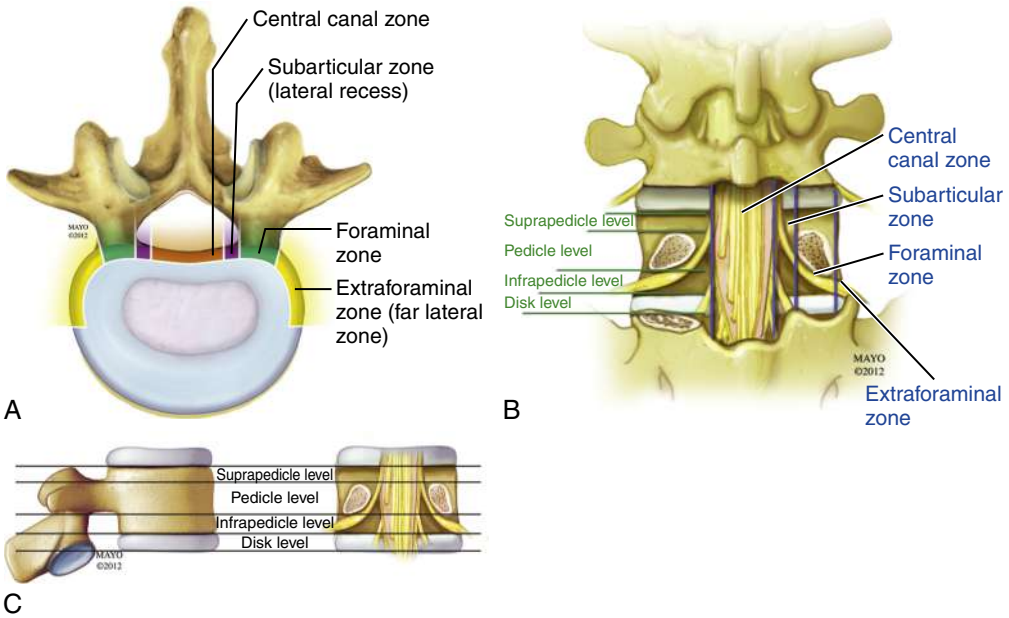
Imaging of patients with radicular pain or radiculopathy should begin with upright radiographs of the involved spine segment. This will establish the enumeration, assess balance and stability, and act as a low sensitivity screen for sinister disease. Advanced imaging may be needed in the setting of intractable radicular pain or progressive neurologic deficit. MRI has long been considered the primary imaging modality in the evaluation of disc herniations, but this has little basis in evidence. No studies compare the current generation CT with MRI technology in the detection and characterization of disc herniations. MRI remains the initial modality of choice largely because of its superior sensitivity and specificity in the detection of sinister disease causal of back or limb pain, which, it must be remembered, is the primary goal of imaging. CT myelography retains a problem solving role in the lumbar region, but it plays a more prominent role in the cervical spine, where its ability to distinguish disc from bone may affect surgical planning.

Imaging Reliability

MRI has shown good reliability in the assessment of disc herniations. Lurie and colleagues[226] analyzed MRI studies of patients with disc herniations from the Spine Patient Outcomes Research Trial (SPORT) trial; interobserver reliability was high ($\kappa = 0.81$) for disc morphology when classified as normal/bulge, protrusion, and extrusion/sequestration. There was moderate interobserver agreement for thecal sac ($\kappa = 0.54$) and nerve root compression ($\kappa = 0.47$). Pfirrmann and colleagues[227] proposed a grading system for nerve root compression. The authors divided the relationship of the herniated disc and the nerve root into four categories: no compromise, contact with the nerve root, deviation of the nerve root, and compression of the nerve root. The intra-observer ($\kappa = 0.62–0.67$) and intra-observer ($\kappa = 0.72–0.77$) reliability results were good. The correlation for a higher grade of nerve root involvement (compression) was better than for low-grade nerve root involvement.

Imaging Observations

MRI T2-weighted images can well display the interface between disc herniations and the thecal sac. The herniated material may be of low T2 signal intensity comparable to the parent disc that has undergone nuclear matrix degradation, but not uncommonly extruded disc material is of higher T2 signal than its parent disc. This may, in part, reflect inflammatory reaction surrounding the extruded material; it can make detection of extruded material in the lateral recesses or foramina challenging on fast spine echo, turbo spin-echo (FSE, TSE) T2-weighted images in which fat is also bright. Comparison with matched T1-weighted images will



• **Figure 20.15** Zones and levels of disc displacement. In the axial plane **(A)** the location of displaced disc material is described by zones. Moving from the midline laterally, these zones are the right or left central zone, demarcated by the medial margins of the facet joints; the subarticular zone (lateral recess), bounded by the medial aspect of the facet joint and the medial aspect of the pedicle; the foraminal zone, bounded by the medial and lateral aspects of the pedicle; and the extraforaminal or far lateral zone, peripheral to the lateral margin of the pedicle. These zones are also illustrated in the coronal plane **(B)**. The displacement of disc material in the cephalocaudal dimension is described by levels, as illustrated in **(B)** and **(C)**.

identify the now dark disc material against the bright fat in the lateral recess or foramina. Occasionally, disc herniations may be associated with a small amount of hemorrhage in the epidural space, which may manifest itself as an epidural process of high T1 and variable T2 signal intensity. This hemorrhage may be related to the pathogenesis of discal cysts, relatively rare cystic lesions in the epidural space, which may present with radicular pain and result from prior disc extrusion and hemorrhage with incomplete resorption.[228]

Ninety percent of lumbar disc herniations occur at the L4 or L5 interspace levels. The vector of disc displacement in most herniations is posterolateral. In the lumbar spine, the exiting nerve passes immediately inferior to the vertebral pedicle and exits the foramen above the interspace level. Therefore most disc herniations do not affect the exiting nerve but rather impinge on the traversing nerve, which exits under the next lower vertebral pedicle. For example, a posterolateral L4–L5 disc herniation results in an L5 radicular pain syndrome or radiculopathy. For a lumbar disc herniation to affect the like numbered nerve, it must be an extrusion with lateral and cephalad migration of disc material into the neural foramen. The greater spatial resolution of CT myelography may identify subtle lateral recess or foraminal lesions that are less clearly seen on MRI.

Contrast material is not typically used when MRI is undertaken to evaluate for causes of radicular pain or radiculopathy except in the presence of red flag features raising concern for infection of neoplasm or prior surgery. Unenhanced imaging can primarily detect the mechanical compression of a nerve, not the inflammatory response, which is also necessary to provoke radicular pain. T2 hyperintensity on STIR or fat-saturated images may identify this reaction. If gadolinium is given, it is often observed that the soft tissue seen on unenhanced images, thought to be herniated disc material, is largely enhancing inflammatory/granulation tissue about a small disc fragment. When confronted with a patient with clinically evident radicular pain or radiculopathy and no evidence of a neural compressive lesion on standard imaging, an enhanced exam may reveal an inflammatory process associated with a disc whose annulus is incompetent.[229] This is described as chemical radiculitis. The neural compressive component of the lesion may only be present on imaging with axial load and physiologic positioning (Fig. 20.16).

Postoperative Imaging

Gadolinium-enhanced MRI does have a well defined role in the evaluation of the postoperative patient. Plain films, CT, and CT myelography are relatively uninformative in the postoperative patient, as they cannot reliably distinguish recurrent disc herniation from epidural fibrosis/scar. Following discectomy, extensive anatomic changes evolve over time, confounding imaging interpretation. Great caution must be used in interpreting MRI within six weeks of surgery.[230] In this time frame, MRI is most useful in the evaluation for hemorrhage, pseudomeningocele, or discitis; evaluation for recurrent disc herniation is tenuous. The diagnosis of postoperative discitis is also complicated by the normal linear enhancement that may be observed in the postoperative disc.[230] As postoperative tissue disruption and edema stabilize, MRI with gadolinium enhancement has been reported to be 96%–100% accurate in distinguishing recurrent disc herniation from scars.[230] Scar or epidural fibrosis enhances rapidly and uniformly following gadolinium administration; disc material does not enhance for the first 20–30 minutes. Early post-gadolinium images in the postoperative patient will show recurrent disc herniation as a non-enhancing zone; enhancing epidural fibrosis may surround this. Extensive scar or epidural fibrosis is in and of itself a negative prognostic sign associated with an increased incidence of postoperative radiculopathy.[231] In the postoperative setting, the thecal sac should be examined for evidence of arachnoiditis. In this condition, the roots of the cauda equina are either clumped together or adherent to the dural tube. The dural tube may even appear empty of roots, which are smoothly scarred to its wall. Roots may exhibit enhancement in this condition.

Imaging Natural History

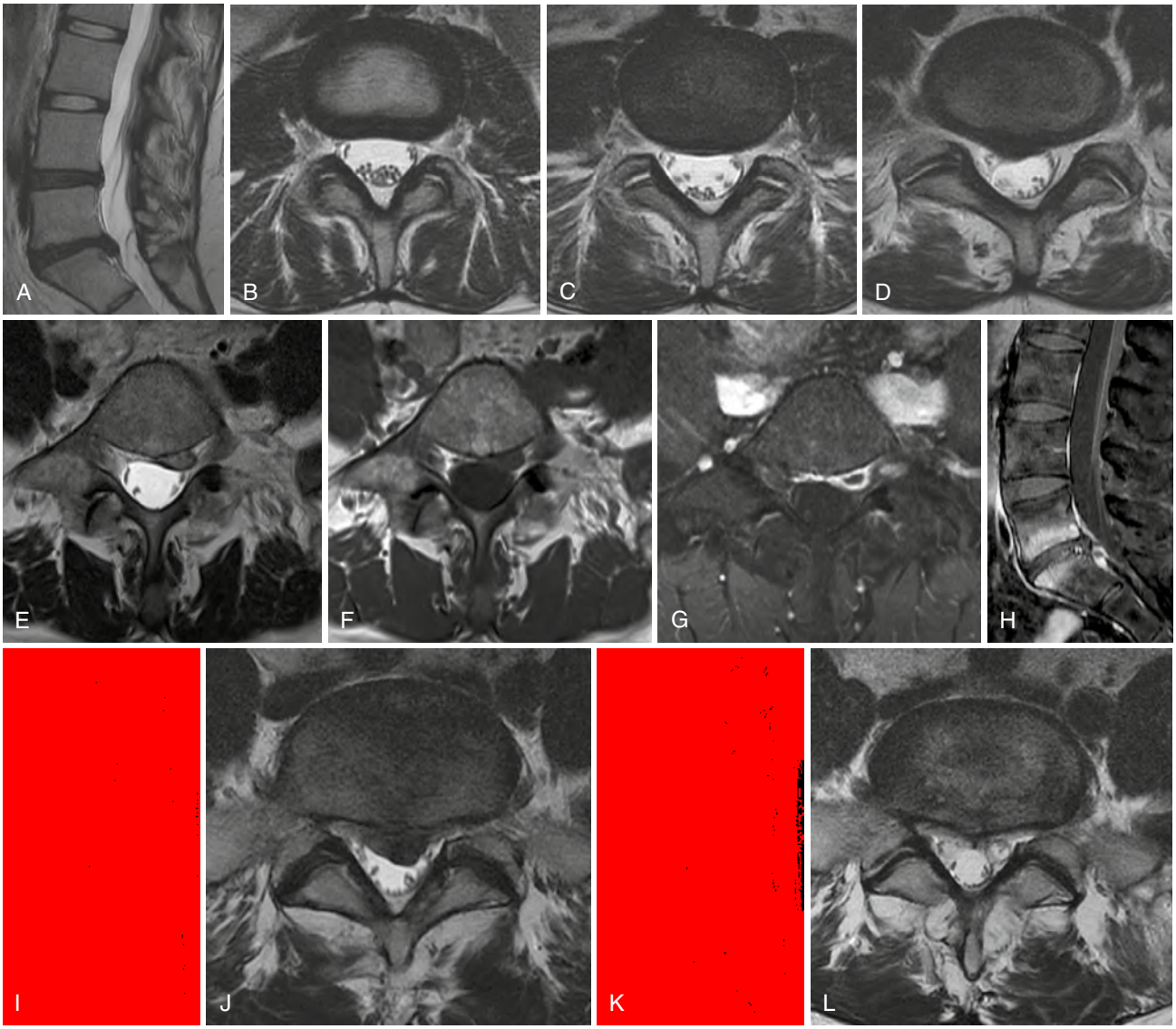
The imaging natural history of disc herniation is often resolution.[232] Large disc herniations, extrusions, and sequestrations, which have entered the highly vascular epidural space, are most likely to undergo resorption mediated by macrophage produced metalloproteases.[233–235] This inflammatory response is integral to the profound pain these patients feel, but it will ultimately resorb the extruded disc material. If the targeted administration of corticosteroids can attenuate the inflammatory response, thus allowing the patient to remain functional, over time, natural history will bear out with resolution of the herniated disc material and the radicular pain syndrome. Contained protrusions and bulges, with intact outer annulus shielding the herniation from the full fury of the immune system, tend not to change.

Validity of Disc Herniation Imaging: Correlation With Symptoms/Signs

The fundamental specificity fault of spine imaging is very evident in the imaging of disc herniations. Modic[61] demonstrated no relationship between herniation type, size, or change over time and patient outcome. Most of the imaging findings observed on an imaging study obtained at presentation with radicular pain will have been present at a time when the patient was asymptomatic.[60] In another study by Masui, disc herniations treated conservatively were followed over seven years.[236] Clinical outcomes were unrelated to the size of the herniation or age changes in the disc. To assign causality to a disc herniation, there must be concordance, a perfect match of the patient's pain or dysfunction syndrome, and the expected detriment caused by an observed herniation. The imager must know the nature of the pain syndrome to identify its likely cause among the distracters of asymptomatic findings. The sensitivity fault is also evident; disc herniations that do not appear to contact neural tissue on recumbent imaging may be compressive under axial load and physiologic posture. Willén and Danielson showed that significant additional information was demonstrated in 14% of sciatica patients on images obtained under extension and axial load, including accentuation of disc herniations, increasing lateral recess or foraminal stenosis, and distention of synovial cysts that contributed to root compression (Box 20.4).[237]

Unusual Manifestations of Disc Disease

Besides their common appearances, locations, and clinical features, intervertebral disc pathologic conditions can have a wide spectrum of manifestations; many of these entities were discussed in an extensive review published in the radiology literature.[238] These include disc herniations in relatively unusual locations, including the dorsal epidural space, the intradural compartment, and the extreme lateral or retroperitoneal zone. Disc herniations may develop cystic change (discal cysts), which may contain blood-fluid levels and even cause benign osseous erosion of adjacent vertebral bodies. On PET-CT, any disc herniations associated with



• **Figure 20.16** Disc herniations. Sagittal T2 magnetic resonance image (MRI) **(A)** and axial T2 images at L3–4 **(B)**, L4–5 **(C)**, and L5–S1 **(D)** discs demonstrate a normal L3–4 disc, a central protrusion at L4–5, and a right central extrusion with caudal migration at L5–S1. Axial T2 **(E)** and T1 **(F)** MRI images at the S1 endplate level demonstrate a left-sided sequestered disc fragment contacting the thecal sac. Fat-saturated T1 axial image **(G)** and sagittal image **(H)** show that much of the apparent disc herniation enhances and is an inflammatory reaction about a small disc fragment. Enhancing Modic I change is present. Another patient with left S1 radicular pain an L5–S1 disc extrusion **(I, J)** was treated with a transforaminal epidural steroid injection with the resolution of pain. He returned four years later with new L5 distribution pain and was reimaged **(K, L)**. Note that the L5–S1 extrusion has completely resolved; **([L]** is at the identical level as **[J])** and a new L4–5 extrusion has developed. The natural history of disc extrusion is resolution.

inflammatory response may manifest with increased uptake, simulating neoplasm. Clinically relevant disc pathology can range from extremely large in size, such as a massive disc herniation occupying over 50% of the central spinal canal, to very tiny, such as a minuscule spiculated/calcified disc that may cause spinal cerebrospinal fluid (CSF) leak and spontaneous intracranial hypotension. Clinical manifestations of the wide spectrum of disc pathology can range from transient with spontaneous resolution, such as acute calcific discitis, which is most common in the pediatric population, to permanently disabling, such as fibrocartilaginous embolism of disc material to the spinal cord with resulting cord infarct.

Radicular Pain

Lateral Recess, Foraminal Stenosis

As the nerve root exits the common dural sac into its root sleeve, it leaves the central spinal canal, passing caudally and laterally into the lateral recess or subarticular zone. Compromise of the lateral recess may be causal of radicular pain or radiculopathy. Lateral recess stenosis is primarily a product of facet joint arthrosis with overgrowth of the SAP. This encroaches on the posterior aspect of the lateral recess, impinging on the exiting nerve root. This

• Box 20.4 Disc Herniations and Radicular Pain

- Radicular pain requires both the compression of neural tissue and an inflammatory response, likely mediated by tumor necrosis factor α.
- Standard imaging can only detect nerve root displacement or compression, which are necessary but insufficient to cause symptoms.
- This is in part the basis of the specificity fault: many disc herniations are asymptomatic.
- Completing the causality of symptoms to a disc herniation requires concordance: there must be a key in lock match between the lesion and the syndrome of pain and neurologic dysfunction.
- The imager must know the nature of the radicular pain/radiculopathy syndrome to consider ascribing symptoms to a disc herniation.
- The natural history of disc herniations is resolution; larger herniations, extrusions, and sequestrations are more likely to resolve.
- There is no relationship between the size, type, or change in disc herniations over time and patient outcomes.
- Decisions regarding surgical intervention must be based on clinical grounds, not imaging appearance.

is best demonstrated on axial MRI or CT myelographic images (Fig. 20.17). These images should be scrutinized to ensure that the nerve root in question is indeed entrapped within the lateral recess rather than simply displaced medially into the central spinal canal. The minimum normal A-P dimensions of the lateral recess have been variably reported as 3 mm to 4 mm.[239] The lumbar level most commonly involved with lateral recess stenosis is the L4–5 interspace level.

As the exiting nerve root continues to progress caudally and laterally under its similarly numbered lumbar pedicle, it enters the foraminal zone. The intervertebral foramen is an inverted teardrop-shaped orifice; the exiting root is situated in the larger, superior aspect of the foramen. An annular bulge or lateral protrusion may intrude into the inferior portion of the neural foramen without causing neural compression. A disc extrusion with cranial migration of disc material into the foramen may contact, displace or compress the exiting root. Other spondylotic phenomena causing foraminal stenosis include osteophytes arising from the posterior margin of the vertebral body or SAP, synovial cysts, or abnormalities of vertebral alignment, including the concavity of a scoliotic curve or spondylolisthesis resulting from spondylolysis or facet arthropathy. Foraminal stenosis is best demonstrated on sagittal MRI images (see Fig. 20.17). The low signal nerve root and accompanying small veins should always be surrounded by high signal fat on T1- or T2-weighted sagittal MRI images. Axial MRI images may also demonstrate foraminal stenosis, although to less advantage.

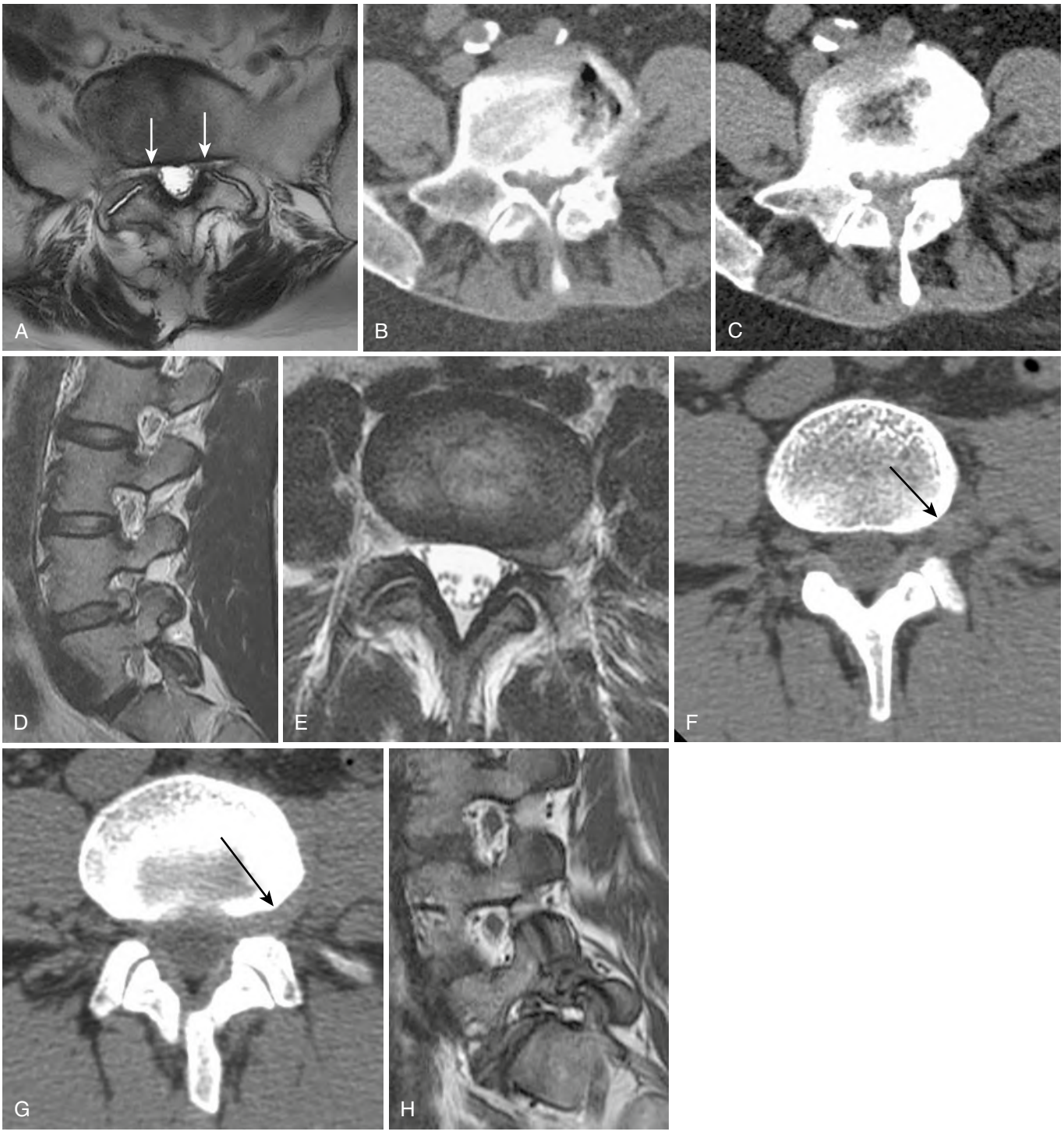
Synovial Cysts

Synovial cysts may accompany facet osteoarthrosis, may be a cause of radicular pain or neurogenic claudication, and may be associated with axial low back pain. Synovial cysts are thought to originate with a degenerative or traumatic defect in the fibrous facet joint capsule, with subsequent herniation of the synovial membrane through the defect. Expansion of the synovial outpouching, no longer constrained by the joint capsule, results in a cystic lesion, which may impinge on adjacent neural structures or simply serve as an imaging marker of capsular pathology. Synovial cysts may retain or potentially lose their communication with the facet joint. Ganglion cysts may have a similar gross appearance but histologically lack a synovial lining; they may be indistinguishable in imaging studies.

Although relatively unusual, synovial cysts are not rare: the series by Doyle and associates[240] demonstrated a prevalence of nearly 10% in a population of patients undergoing MRI for back or leg pain. In this series, anterior or intraspinal cysts, often arising from the superior recess, had a prevalence of 2.3%; posterior or extraspinal cysts were more common with a 7.3% prevalence. Synovial cysts are prevalent in the elderly population, with an average age of 63 years in Métellus' study,[241] 61 in Apostolaki's[242] study population, and 66 years in the large surgical series of Lyons.[243] Reported male-to-female ratios are inconsistent, varying from a 1:1 ratio in the Lyons series to 1.2:1 in the Métellus series and 1:2 in the Apostolaki study; Doyle noted a female predominance in posterior cysts only. Synovial cysts are far more common in the lumbar region than in the thoracic or cervical spine. The literature has consistently shown that 60%–70% of lumbar synovial cysts will be at the L4/5 level, followed in relative order by L5/S1, L3/4, and L2/3. Anterior or intraspinal synovial cysts most commonly occur posterolaterally to the thecal sac in close association to the facet joint. They may be embedded in the ligamentum flavum. Uncommonly, cysts may be located directly dorsal to the thecal sac, laterally within the neural foramen, or in a far lateral or extraforaminal site. Far lateral synovial cysts typically arise from the superior recess of the joint, which extends over the superior margin of the SAP; the communication with the joint will not be seen on an axial image but may be apparent on sagittal images.

Synovial cysts often arise from facet joints exhibiting significant arthrosis, with sclerosis, osteophytes, and increased joint fluid, although most joints with arthrosis do not produce cysts. Segmental hypermobility is postulated as an underlying cause of synovial cysts. This is supported by the strong association with the most mobile lumbar segment (L4/5) and the frequent (42%–65%) association with degenerative spondylolisthesis.[242] Disc age-related changes are commonly present at the level of the cyst. Metellus[241] also noted that most cysts arise from joints with a predominant sagittal orientation; this orientation is also associated with segmental instability.

Synovial cysts may be detected by CT, CT myelography, or MRI; MRI is thought to be the most sensitive (Fig. 20.18). Calcified cysts may rarely be seen on plain radiographs. Synovial cysts have great variation in their histology, with corresponding variation in their imaging appearance. Synovial cysts may be thin-walled collections of pure synovial fluid, or they may be complicated by varying degrees of chronic or acute hemorrhage and inflammation. Pure cysts have a high T2 signal, equal to or exceeding that of cerebrospinal fluid (CSF), with a corresponding low T1 signal and a thin, low signal wall. With chronic hemorrhage, cyst contents may develop a high T1 signal (methemoglobin) and a variable T2 signal; the wall often enhances with gadolinium. In the presence of chronic inflammation and calcification, the wall may become quite thick, with a very low T1 and T2 signal. On CT, calcification is variably observed, and cyst contents range from hypodense to slightly hyperdense relative to muscle. Changes in arthrosis in the adjacent facet joint are typical, including abnormal marrow signal (T2 hyperintensity, T1 hypointensity) in the articular processes and pedicle. Direct communication with the facet joint is not always demonstrable on either CT or MRI. Synovial cysts may not be evident on recumbent CT or MRI imaging, as the synovial fluid recedes into the joint space, collapsing the cyst; when the patient assumes axial load, the joint surfaces are opposed, driving the fluid into the cyst, which then exerts mass effect on neural



• **Figure 20.17** Subarticular Zone (Lateral Recess) and Foraminal Compromise. Axial T2 MRI image **(A)** at the S1 superior endplate demonstrates a widely patent central spinal canal but severe bilateral subarticular zone stenosis *(arrows)* resulting from facet hypertrophy. Consecutive CT images **(B, C)** at the L5 pedicle level in another patient show severe central spinal canal stenosis and severe subarticular zone stenosis primarily caused by endplate osteophytes. T2 sagittal and L4–5 disc axial images **(D, E)** in a patient with left anterior thigh pain reveal a left foraminal disc extrusion, displacing the dorsal root ganglion (DRG) superiorly and laterally. Axial CT images **(F, G)** in another patient with left L4 radicular pain also demonstrate a left L4 foraminal and extraforaminal extrusion *(arrows)* effacing the fat about the exiting L4 DRG and ventral ramus. A final patient with L5 spondylolysis **(H)** demonstrates the typical S-shaped foraminal stenosis at L5–S1 seen in this setting. Note normal foramina at L3–4 and L4–5 with abundant fat surrounding the DRG and small veins.

• **Figure 20.18** Synovial cysts. Typical bilateral L4 intraspinal synovial cysts **(A)** compress the thecal sac on a T2 axial image. A different patient **(B)** demonstrates a synovial cyst in the left L5–S1 neural foramen as well as a posterior extraspinal cyst. Another patient with right L5 radicular pain demonstrates an L4–5 synovial cyst on sagittal **(C)** and axial **(D)** T2 images. The patient underwent a right L5 transforaminal epidural steroid injection and an intra-articular injection of the facet joint/cyst. Her pain resolved. She presented four years later with axial pain. Magnetic resonance T2 sagittal **(E)** and axial **(F)** images show a new L5 compression fracture; the synovial cyst has resolved. A final patient demonstrates an irregular thick-walled cyst *(arrows)* arising from the left 3–4 facet **(G, H, I).** Note the T1 hyperintensity **(H).** Computed tomography **(J)** shows the cyst is calcified *(arrow).*

elements. Not infrequently, synovial cysts will fill when the joint is pressurized by intra-articular injection, despite no evidence of their existence on advanced recumbent imaging. The imaging differential diagnosis includes conjoined nerve root sleeves, sequestered disc fragments, cystic nerve sheath tumors, and degenerative cysts of other origins, such as pseudobursae in Baastrup's disease.

Anterior or intraspinal synovial cysts often present as lesions causing unilateral radicular pain or contributing to neurogenic claudication. Anterior synovial cysts may cause focal neural compression in the lateral recess, foramen, or extraforaminal space, or they may contribute to central spinal canal stenosis. Posterior cysts do not cause neural compression but may be associated with

axial pain and be an imaging sign of facet capsular disease. Synovial cysts may regress spontaneously. Radicular pain resulting from synovial cysts may be treated by an injection of corticosteroid into the facet joint bearing the cyst, with a transforaminal epidural steroid injection at the same procedural setting. This strategy successfully allowed 50% of patients to avoid surgical injections in a series by Sabers and colleagues.[244] Other non-operative therapies have included aspiration, fenestration, or rupture of cysts under CT or fluoroscopic guidance. A large case series (n = 101) of percutaneous cyst rupture showed surgical sparing in about 50% of cases.[245] A series of 85 CT-guided direct synovial cyst aspiration and fenestration procedures by Shah and colleagues similarly showed that 56% of patients had partial or complete long-term relief without the need for a subsequent operation.[246] A similarly sized (n=110) retrospective review of CT-guided cyst rupture demonstrated that cysts of high or intermediate T2-signal intensity were more likely to be successfully ruptured than T2-hypointense cysts; the high signal intensity cysts also had lower rates of subsequent surgery.[247] Surgical resection of synovial cysts generally has a favorable outcome, but it may require facetectomy, laminectomy, and possible fusion. Even after surgery, synovial cysts can recur.

Cervical Disc Herniations

The cervical intervertebral discs differ structurally from the lumbar disc. The cervical discs are thicker anteriorly than posteriorly and have a less well defined nuclear/annular structure. There is no discrete annulus at the posterior disc margin. The cervical discs function less to disburse axial load. They undergo maturational change with age; intradiscal T2 signal loss is a poor predictor of axial pain. Cervical radicular pain or radiculopathy is less common than lumbar symptomatology. Cervical radicular pain is most commonly caused by foraminal compromise of multifactorial origin: uncovertebral joint and facet hypertrophy, loss of disc space height, and less frequently disc herniation. In a population-based study in Rochester, Minnesota, disc herniations were causal of only 22% of cervical radiculopathies.[248] The C6 and C7 nerves were most commonly affected. As in the lumbar region, the vector of herniation is usually posterolateral, but as the cervical nerves exit low in the foramen, a herniation will likely affect the exiting nerve, not the traversing nerve. For instance, the C6 nerve exits low in the C5–6 neural foramen; a herniation at this segment is expected to impinge on the C6 nerve.

The natural history of cervical disc herniations parallels the lumbar region. Cervical disc herniations may undergo spontaneous regression. As in the lumbar region, extrusions, migrated disc material, and laterally situated disc herniations are more likely to undergo spontaneous regression. As most lesions causing cervical radicular pain are not purely soft disc but are, at least in part, osseous, overall regression of the root compressive lesion is less likely than in the lumbar region. MRI remains the primary advanced imaging modality, but CT myelography may play a larger role. It provides the best spatial resolution, critical in the narrow confines of the cervical region, and excels at discriminating bone from soft disc, which may alter the surgical approach (Fig. 20.19).

Thoracic Disc Herniations

Symptomatic thoracic disc herniations are rare; only 1%–2% of all disc surgeries are performed in the thoracic segment.[249] The expected specificity fault applies; age-related disc changes are ubiquitous, and herniations are often asymptomatic. The majority of disc herniations occur in the mid and lower thoracic region. In the surgical series by Stillerman,[250] the T8–T11 levels were most commonly affected. In this series, 76% of patients presented with pain, 61% with either motor or sensory dysfunction, and 24% with bladder dysfunction. Nearly two-thirds of the disc herniations showed evidence of calcification on CT imaging. At surgery, 7% showed intradural extension. Thoracic disc herniations involving the conus can mimic lumbar radicular pain; MRI studies of the lumbar spine should always extend to the conus on the sagittal sequences.

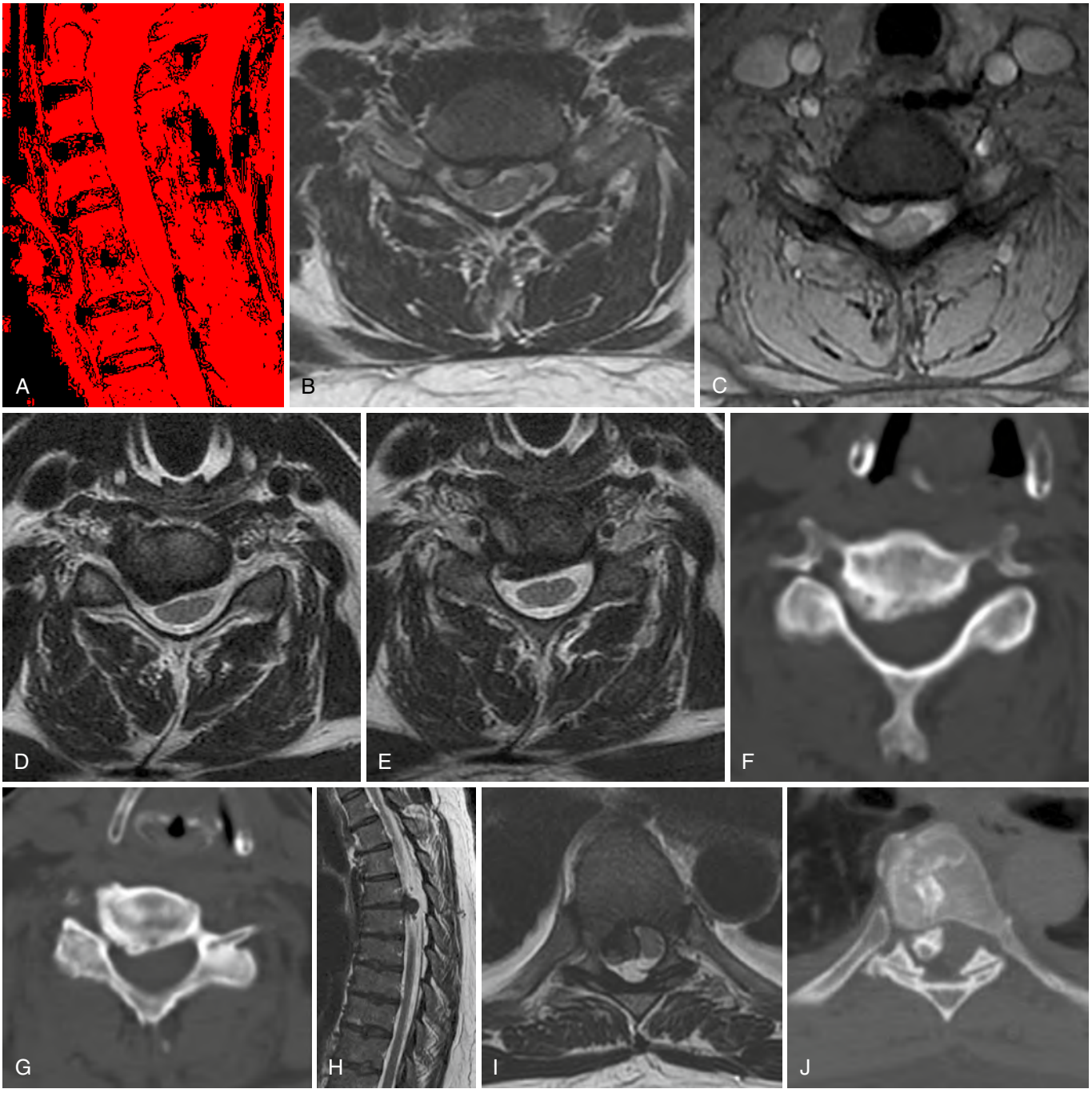
Imaging of thoracic radicular pain should involve MRI or CT myelography. CT myelography has the greatest spatial resolution and may better demonstrate the presence of calcification within thoracic discs. MRI can detect signal abnormality within the cord, which may identify cord edema or venous hypertension, verifying the physiologic significance of a disc herniation. All imaging evaluations for thoracic disc disease must include careful enumeration of the segmental level involved. If a lesion that may require surgical or percutaneous intervention is detected, the imaging study should be extended to include sagittal images from the sacrum to the skull base. Communication between radiologists, surgeons, and/or spine interventionalists is critical to avoid wrong segment interventions. Image guided marker (gold seed) placement is used by some centers to ensure correct level surgery.

Degenerative Spondylolisthesis

Spondylolisthesis refers to the abnormal anterior or posterior displacement of one vertebral body relative to another. Displacement caused by defects in the pars interarticularis (spondylolytic spondylolisthesis) will be discussed later. Degenerative anterolisthesis is the anterior displacement of a vertebral body relative to the body immediately caudal to it. The etiology of degenerative anterolisthesis is primarily facet joint arthrosis, often with a relative sagittal orientation of the facets. Disc structural failure is also necessary. Degenerative anterolisthesis may be present in 4%–14% of elderly patients.[251] Anterolisthesis is most frequent at the L4 level, with less common occurrence at L5, followed by L3. It is significantly more common in women than in men.[251] Radiographic findings of degenerative anterolisthesis include the obvious displacement itself, joint space narrowing and sclerosis in the associated facets, and findings of intervertebral osteochondrosis, including a loss of disc space height, gas within the disc, and subchondral sclerosis.

Degenerative retrolisthesis describes the posterior displacement of the index vertebral body relative to that below it; the primary causative process is intervertebral osteochondrosis. As there is a loss of disc space height, the oblique orientation of the facet results in the more superior vertebral body gliding posterior relative to its inferior counterpart. Degenerative retrolisthesis is most commonly seen at the L2 interspace level, with less common occurrence at L1, followed by L3. There is no significant gender difference.

Degenerative spondylolisthesis may be associated with axial low back pain. The Kauppila study showed that patients with degenerative spondylolisthesis had a higher prevalence of daily low back symptoms.[251] However, there was no increased disability in spondylolisthesis patients relative to controls. In this study, the overall incidence of degenerative spondylolisthesis approached 20%. Degenerative spondylolisthesis carries with it the risk of neural element compromise with secondary central spinal canal stenosis, lateral recess stenosis, or foraminal compromise.



• **Figure 20.19** Cervical and thoracic disc herniations. A patient with prior C5–6 anterior cervical discectomy and fusion presents with new right C7 distribution radicular pain. Sagittal T2 image **(A)** shows disc extrusion with caudal migration from the adjacent C6–7 segment. Note that the extruded material has a higher T2 signal than the parent disc, perhaps a reflection of the inflammatory response. Axial fast spine echo (FSE) T2 **(B)** and gradient echo **(C)** axial images at the C6–7 interspace well demonstrate the extrusion. In another patient with a right C6 radiculopathy, axial FSE T2 images **(D, E)** at the C5–6 interspace suggest a disc-osteophyte complex and uncovertebral joint osteophytes compromise the right C5–6 foramen. The primary osseous nature of the process is confirmed on computed tomography (CT) images **(F, G).** In the cervical spine, compressive lesions are more likely to be osseous than soft disc alone. Thoracic disc extrusion in a 51-year-old woman with progressive thoracic myelopathy is shown in images **H, I,** and **J**. Sagittal T2 magnetic resonance (MR) image **(H)** shows large T5–6 disc extrusion. Low T2 signal suggests calcification. The cord is displaced and compressed by the right-sided extrusion on the T2–weighted axial MR image **(I)**. Axial CT image **(J)** demonstrates coarse calcification in the disc extrusion. Note the linear defect with marginal sclerosis in the endplate, a finding often accompanying disc herniations.

Spinal Stenosis: Lumbar Neurogenic Intermittent Claudication

Lumbar spinal stenosis is an imaging observation; it may give rise to the clinical syndrome of neurogenic intermittent claudication (NIC). NIC is the most common reason for spine surgery in patients over 65 years of age.[252] The hallmark is the induction of gluteal and lower extremity pain with upright exercise or specific postural positions and palliation by forward flexion, sitting, or recumbency. The most common symptoms in patients with lumbar spinal stenosis are back pain (prevalence of 95%), claudication (91%), leg pain (71%), weakness (33%), and voiding disturbances (12%).[253] There may be a paucity of physical findings, even in the presence of symptoms.

Despite its significance, data on the natural history or prevalence of NIC are scarce. Kalichman and colleagues utilized data from the Framingham study to establish the prevalence of congenital and acquired lumbar central spinal canal stenosis in a community population.[254] Using the AP dimension of the central spinal canal derived from CT studies (12 mm = relative stenosis, 10 mm = absolute stenosis), they noted congenital central spinal canal narrowing of relative degree in 4.7% of the population and absolute stenosis in 2.6%. Acquired stenosis was identified in 22.5% (relative) and 7.3% (absolute) of individuals. Their literature review noted that the prevalence of acquired lumbar stenosis ranged from 1.7%–13.1%. The prevalence of acquired stenosis (absolute) increased from 4% in patients younger than 40 years old to 14.3% in patients older than 60 years. The North American Spine Society (NASS) 2011 evidence based guidelines on the diagnosis and treatment of spinal stenosis suggest, in the absence of reliable evidence, that the natural history of patients with clinically mild to moderately symptomatic degenerative stenosis is favorable in one-third to one-half of patients.[53] In patients with mild to moderately symptomatic stenosis, rapid or catastrophic neurologic decline is rare.

Pathophysiology

The pathogenesis of NIC in lumbar spinal stenosis has been a subject of investigation for half a century. Verbiest initially described mechanical compression of the nerve roots of the cauda equina as a cause of NIC in 1954.[255] Subsequent investigators have postulated that arterial and venous ischemia, perhaps exacerbated by restriction of CSF flow (which participates in nerve root nutrition), are contributors to the clinical syndrome. The current preponderance of evidence favors venous congestion secondary to mechanical compression. This hypothesis emphasizes the importance of multiple levels of compression and the physiologic effects of lumbar extension. Both of these observations have significant relevance to imaging.

The animal work of Takahashi and Olmarker demonstrated that two zones of modest compression in the cauda equina would dramatically reduce blood flow to the intervening nerve segment because of venous congestion; this venous congestion could precipitate neural dysfunction.[256,257] Kobayashi examined cauda equina histology after the application of modest stenosis (30% of the cross-sectional area) to the dural tube.[258] The cauda equina demonstrated congestion and dilatation of intraradicular veins and an inflammatory cellular infiltrate. There was disruption of the blood–nerve barrier, both at the compression site and in more distant sites of Wallerian degeneration. The necrotic debris created by Wallerian degeneration stimulated macrophage activity generating inflammatory molecules such as interleukin-1 and TNFα. Macrophages stimulate cytotoxic activity by the release of nitric oxide and proteases. They are considered the chief effector cells causing inflammatory neuritis that results in aberrant ectopic neural discharge and conduction disturbance, leading to the pain and neural dysfunction of NIC.[258]

Multiple sites of venous congestion are key to this model of NIC; it is supported by clinical studies. Sato demonstrated that patients with two-level central spinal canal stenosis were significantly more likely to exhibit NIC than were patients with a single level of canal compromise.[259] In two-level stenosis, the symptomatic expression most closely matched the radicular distribution of the more caudal of the two stenotic levels; in patients with compromise at the L3 and L4 disc levels, the pain pattern matched that of the traversing L5 roots.[259] Porter and Ward noted that the compression sites might be either in the central spinal canal or in the neural foramina.[260] In their cohort of 49 patients with NIC, 94% had either multilevel central spinal canal stenosis or central spinal canal plus neural foraminal stenosis. The work of Morishita emphasized the importance of the neural foramen as a potential zone of compression, particularly with dynamic changes in posture.[261] Even without demonstrable foraminal compromise by imaging in a neutral position, in lumbar extension, intraforaminal pressures exceeded venous pressure, and neural dysfunction was documented by electromyography (EMG). All levels of neural compromise, central, lateral recess, and foraminal are potentially significant and must be detected by imaging.

Congenital Central Spinal Canal Stenosis

A relatively small proportion of patients with clinical NIC will have developmental narrowing of the lumbar central spinal canal as a predisposing factor, with only modest spondylotic changes necessary to produce clinical symptoms. Singh and colleagues studied the morphologic characteristics of a cohort of surgically treated patients carrying the clinical diagnosis of congenital lumbar stenosis.[262] They noted that these patients had a significantly shorter pedicle length and a smaller cross-sectional central spinal canal area when compared with age- and sex-matched controls. The patients with a congenitally narrowed lumbar central spinal canal typically exhibit these morphologic characteristics over several vertebral segments, maximal at the L3 level. This contrasts with purely acquired stenosis, which is often more focal, particularly at the L4 disc level. Congenital central spinal canal stenosis patients tend to present at a younger age (40–50 years) and with less spondylotic change than typical.

Acquired Spinal Stenosis

Most patients presenting with NIC have acquired spondylotic change as their primary cause of central spinal canal, lateral recess, or foraminal compromise. The changes that result in compromise of the central spinal canal are rooted in the three-joint structure of the spine motion segment: the disc and the paired facet joints. In the anterior column, degradation of the disc nuclear matrix places an excessive load on the posterior annulus, and annular failure results in posterior endplate osteophytes and disc herniation. These changes encroach on the ventral aspect of the central spinal canal or lateral recesses. Loss of disc space height obligates narrowing of the neural foramina and contributes to increased facet load and ultimately arthrosis; facet capsular hypertrophy and

SAP osteophytes compromise the lateral recesses. Synovial cysts, particularly at the L4 level, may contribute to the central spinal canal, lateral recess, or foraminal compromise. The reduced height of the segment and the loss of elasticity of the ligamentum flavum result in its buckling centrally as a dominant cause of the loss of cross-sectional area of the central spinal canal. The ligamentum flavum may also thicken, although it is unclear if this represents true hypertrophy. These several anterior and posterior column phenomena conspire to narrow the central spinal canal, most commonly at the L4–5 disc level, followed by L3–4, L5–S1, and L1–2.[263]

Several measurable parameters could quantify the degree of stenosis depicted by radiography, myelography, CT, or MRI. Verbiest, in his early descriptions of the entity of spinal stenosis, suggested that a 10–12 mm AP diameter of the dural sac on conventional myelography constituted relative stenosis, with a measurement of <10 mm denoting absolute stenosis.[255] Steurer, in a 2011 review, surveyed the numerous measurements applied by various authors in the intervening decades in 25 unique studies and four systematic reviews.[239] The most common descriptors of central stenosis include the AP dimension of the osseous canal or the dural sac and the cross-sectional area of the dural sac. A dural sac AP dimension of <10 mm or a dural sac cross-sectional area of <100 mm^2 constitutes stenosis. Descriptors of LR or subarticular stenosis include the height and the lateral recess angle. Height is defined as the shortest distance between the most anterior point of the SAP and the posterior vertebral body, and the LR angle is the angle formed by the posterior vertebral body and the pars interarticularis. LR stenosis is typically defined as height <3 mm or angle <30 degrees. Descriptors of foraminal stenosis most commonly used suggest a diameter of ≤2–3 mm to indicate stenosis. In keeping with the prior discussion on specificity limitations of imaging findings, a recent investigation demonstrated that the severity of lumbar spinal stenosis as depicted by advanced imaging (CT or MRI) is not associated with differential responses after epidural steroid injections.[264]

The multiplicity of quantitative parameters suggests that no single measurement has proven satisfactory. The very notion of a readily quantifiable measure of stenosis may be flawed. There is a wide normal variation in the central spinal canal and dural tube diameters; an assessment of stenosis must address not simply diameter or cross-sectional area but the crowding or compression of neural tissue. The semiquantitative criteria advanced in 2001 by Fardon and Milette[224] simply defines reduction in the expected area by less than one-third as mild, by one-third to two-thirds as moderate, and by greater than two-thirds as severe. This allows a subjective judgment of neural compression at the potential cost of reliability. Lurie and associates studied the reliability of the subjective grading of stenosis of the central spinal canal, lateral recesses, and neural foramina and measurement of the central spinal canal and dural sac area aided by specific definitions and imaging examples of the criteria.[265] Stenosis was subjectively rated as none, mild, moderate, and severe using the Fardon and Milette definitions; nerve root compromise in the foramen was categorized as none, touching, displacing, or compressing. Inter-reader reliability in assessing the central spinal canal was substantial, with a $\kappa = 0.73$. There was moderate to substantial reliability for foraminal stenosis and nerve root impingement ($\kappa = 0.58$ and 0.51, respectively). Reliability for subarticular stenosis was only moderate at $\kappa = 0.49$. These results emphasize the importance of a clear definition of criteria for reliably grading stenosis by subjective scales.

Other imaging observations have been employed in an attempt to identify significant stenosis. The observation of nerve root redundancy as a qualitative marker of central spinal canal compromise dates from the original description of the entity of spinal stenosis by Verbiest.[255] This is presumed to originate from mechanical entrapment of the root at the site of compression, with subsequent elongation of the nerve above this site under the tensile stress of physiologic flexion and extension motion. Some of these prominent structures may also represent dilated veins. Although frequently observed, this sign has been subjected to little study. Redundant nerve roots are present in 34%–42% of surgical candidates with clinical NIC.[266] In a 2007 study by Min and colleagues, redundant nerve roots were more commonly observed in older patients, but there was no significant association with the duration of symptoms, diameter of the central spinal canal, preoperative symptom intensity, or surgical outcomes.[266] There was a nonsignificant trend toward poorer surgical outcomes in patients with redundant roots. The prevalence of redundant nerve roots in patients with lumbar spinal stenosis has been shown to be body position dependent; a study using an upright MRI scanner demonstrated the prevalence increased from 17% during flexed sitting to 80% during standing.[267]

A 2010 study by Barz first described the "nerve root sedimentation sign" (NRSS) as a marker of symptomatic NIC.[268] In patients without central spinal canal compromise, the roots of the cauda equina lie in the dorsal aspect of the dural sac on supine MRI imaging. A positive NRSS was defined as the absence of nerve root sedimentation to the dorsal dural sac on at least one axial MRI image at a level above or below the zone of compression; the two nerve roots leaving the dural sac at the next most caudal segment are exceptions. This retrospective study included 200 patients: 100 patients with low back pain but without clinical NIC, and a dural cross-sectional area (DCSA) of >120 mm^2 and a cohort of 100 patients with clinical NIC, a maximum walking distance of less than 200 m, and a DCSA of less than 80 mm^2 on at least one level. There was no correlation between the smallest DCSA and patient disability as measured by ODI. However, an NRSS was identified in 94 of the patients in the NIC cohort but none of the low back pain group.

Since then, multiple other studies have assessed the role of the NRSS as an imaging marker in patients with NIC.[269] Although some heterogeneity was noted in the results of these studies, two meta-analyses demonstrated NRSS to be an accurate imaging marker of spinal stenosis.[270,271] The latter, and more comprehensive, meta-analysis assessed the diagnostic capabilities of the NRSS in the diagnosis of spinal stenosis, based mainly on the presence of NIC. Using the results of 14 prior studies, the authors found that identification of an NRSS had high sensitivity (84%) and specificity (95%) for the diagnosis of clinical sequelae of spinal stenosis.[270] Piechota et al. recently found that 89% of patients with an NRSS presented with NIC.[272] In addition, patients with an NRSS have been shown to have higher intraoperative epidural pressure, adding evidence that the sign is related to tethering of nerve roots at the level of stenosis.[273] The prognostic usefulness of the NRSS in predicting surgical outcomes remains uncertain. Barz et al. found that the presence or absence of the sign did not impact the outcome (based on ODI) in surgically decompressed patients; nonoperative patients with an NRSS had more limited improvement than those without the sign.[274]

Given the specificity challenges of purely anatomic imaging, the more physiologic parameter of gadolinium enhancement may have a role. This is not a new observation; in 1993, Jinkins

observed abnormal intrathecal nerve root enhancement at the site of stenosis on enhanced MRI in patients with NIC.[275] He postulated this represented a breakdown of the blood-nerve barrier at sites of nerve root injury with subsequent Wallerian degeneration. This has been elegantly confirmed in a canine model by the work of Kobayashi.[258] Histologic examination demonstrated congestion and dilatation of intraradicular veins and inflammatory cellular infiltrate at sites of gadolinium enhancement. Gadolinium enhancement may provide added specificity in the correlation of imaging and the clinical symptomatology of NIC; this remains to be proven in clinical studies (Fig. 20.20).

Specificity of Imaging Findings

The ultimate challenge in establishing the utility of diagnostic imaging in the diagnosis of NIC is the lack of a gold standard against which to measure imaging parameters. Surgical findings may be subjective. Clinical outcomes depend highly on the technical success of the instituted surgical therapy and the outcome instruments used in any such measurement.

The specificity fault in imaging of central spinal canal stenosis can be seen in studies of asymptomatic volunteers. Boden and associates noted significant lumbar central spinal canal stenosis on MRI in 21% of asymptomatic subjects over the age of 60.[18] Jarvik and colleagues demonstrated that asymptomatic stenosis on MRI increases in prevalence with age: moderate to severe central spinal canal stenosis was observed in 7% of subjects aged <45 years; in 6% of subjects aged 45–55 years; in 11% of subjects aged 55–65 years, and in 21% of subjects aged >65 years.[19]

Against this background of asymptomatic central spinal canal narrowing, numerous conflicting studies have attempted to establish a relationship between imaging quantitation of central spinal canal or dural size and clinical expression of NIC. For example, Hamanishi and colleagues showed that a decrease in the DCSA to less than 100 mm² at more than two of three lumbar levels (L2–3, L3–4, L4–5) was highly associated with the presence of clinical NIC.[276] For each study showing such an association, several others refute it. Sirvanci examined patients undergoing decompressive surgery for NIC.[277] Morphologic stenosis was assessed by DCSA (>100 mm^2: normal; 76–100 mm^2: moderately stenotic; <76 mm^2: severely stenotic) and a four-point grading of subarticular and foraminal stenosis. There was no correlation between the measured parameters in any spine compartment and patient disability as measured by ODI. This applied both to patients with multilevel central stenosis and a subset with degenerative spondylolisthesis. The NASS guidelines[53] conclude there is insufficient evidence to recommend for or against a correlation between clinical symptoms or function and the presence of anatomic narrowing of the central spinal canal on cross-sectional imaging.

Sensitivity of Imaging Findings

There is also a basic sensitivity flaw in advanced imaging. NIC is by definition intermittent; most patients with NIC report exacerbation of symptoms with extension and weight bearing. It is well known that the cross-sectional area of the central spinal canal, subarticular zone or lateral recess, and neural foramina are maximized with flexion positioning; the dimensions of these structures diminish with extension and axial load. Intradiscal pressures are significantly lower when one is in a recumbent position than when sitting or standing. A 2009 study by Hansson and associates identified the ligamentum flavum as the greatest dynamic contributor to central spinal canal compromise with axial load and extension.[42] The average cross-sectional area of the central spinal canal diminished by 23 mm² at the L3 disc level and 14 mm² at the L4 level under load. The ligamentum flavum was responsible for 50% of the reduction at the L3 level and 85% of the reduction at the L4 level. Madsen and associates attempted to distinguish between the effects of axial load and extension. Their work suggested that lumbar spine extension is the dominant cause of reduction in DCSA in standing patients.[43] Mechanisms circumventing this flaw include upright axial loading devices, the technologically immature upright MRI, and cone-beam CT myelography (Box 20.5).

Thoracic Spinal Stenosis

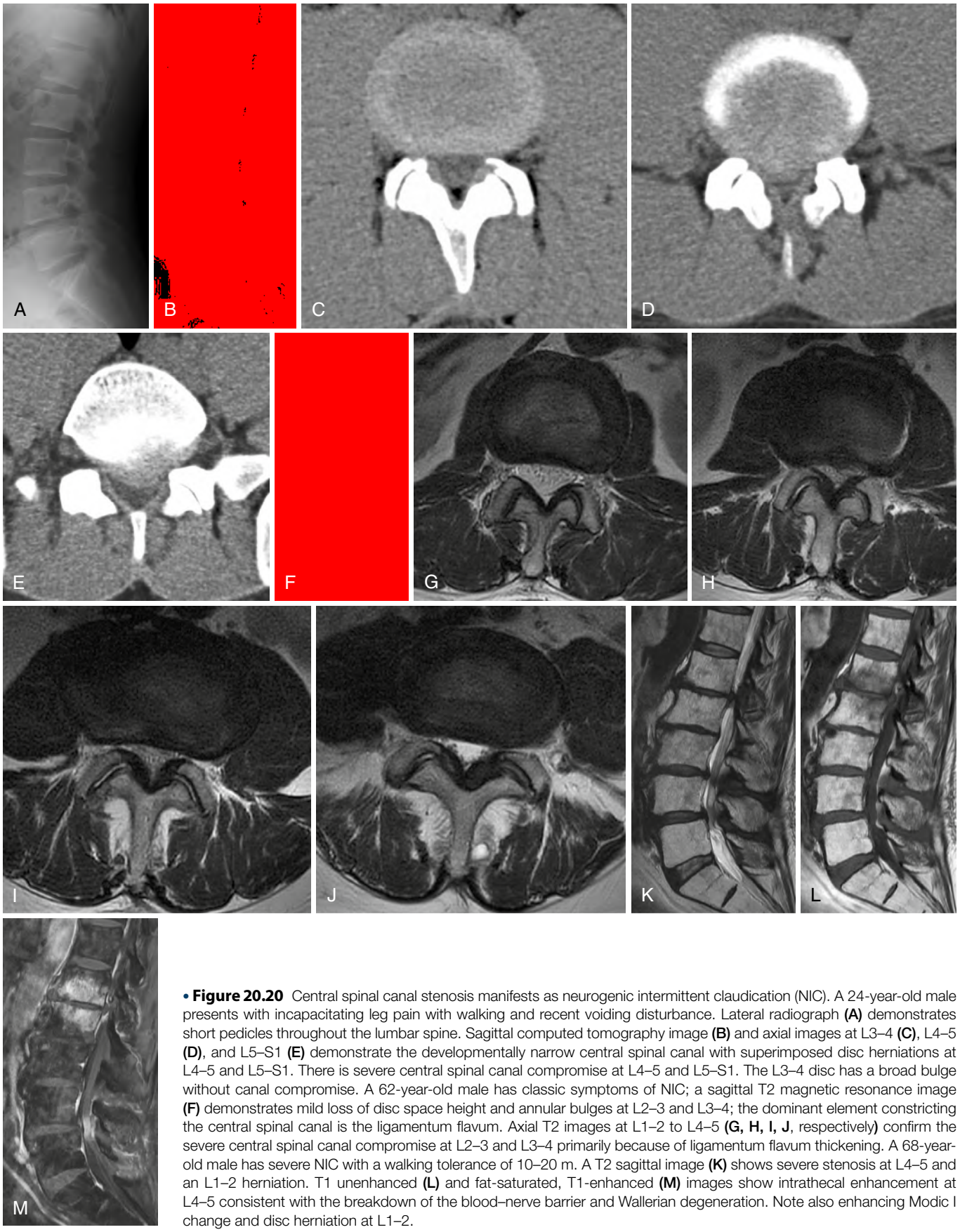
Symptomatic central spinal canal stenosis in the thoracic segment of the spine resulting from age-related change is far less common than in the cervical and lumbar regions, likely because of the added mechanical stability imparted by the rib cage. Systemic disease accounts for a correspondingly greater proportion of cases. Systemic processes leading to thoracic central spinal canal compromise include achondroplasia, osteochondrodystrophy, Scheuermann's disease, diffuse idiopathic skeletal hyperostosis (DISH), and Paget's disease.

Compromise of the thoracic central spinal canal may manifest clinically as myelopathy, radiculopathy, or a mixed presentation. The segmental level of canal compromise is most commonly reported to be in the lower thoracic region. Thoracic spine mobility, particularly flexion-extension motion, is the greatest near the thoracolumbar junction, and is likely the biomechanical mechanism underpinning this age-related pathology distribution. Posterior element age-related changes play a greater role than spine mobility in the genesis of thoracic central spinal canal compromise. This takes the form primarily of unilateral or bilateral facet joint hypertrophy. Thoracic disc herniations or disc-osteophyte complexes may also contribute. The ventral and dorsal contributions to thoracic central spinal canal compromise are visible on CT, CT/myelography, and MRI.

Other causes of thoracic central spinal canal stenosis include ossification of the thoracic ligamentum flavum (OLF), a well-recognized cause of thoracic stenosis in the Asian population but rare among Caucasian subjects. Epidural lipomatosis is a rare cause of central spinal canal compromise in the thoracic or lumbar spine. It may be idiopathic or secondary to endogenous or exogenous steroid excess. Obesity is a common factor in both groups. Excess epidural fat acts as a mass compressing the dural sac, most commonly from a dorsal vector in the thoracic region; it is more likely to be circumferential in the lumbar region.

Cervical Stenosis: Cervical Spondylotic Myelopathy (CSM)

CSM is the most common cause of spinal cord dysfunction in patients over 55 years old.[278] Stookey originally described cervical spondylotic myelopathy in 1928.[279] Although its pathophysiology remains incompletely understood, it is widely acknowledged to involve static factors causing stenosis of the cervical canal and dynamic factors causing repetitive cord injury.[278] These mechanical factors both directly injure neural tissue and initiate secondary ischemia, inflammation, and apoptosis. The histologic characteristics in the cord in CSM include cystic cavitation and gliosis of the central gray matter and demyelination of the medial portions of the white matter long tracks. There is Wallerian degeneration in



• **Figure 20.20** Central spinal canal stenosis manifests as neurogenic intermittent claudication (NIC). A 24-year-old male presents with incapacitating leg pain with walking and recent voiding disturbance. Lateral radiograph **(A)** demonstrates short pedicles throughout the lumbar spine. Sagittal computed tomography image **(B)** and axial images at L3–4 **(C)**, L4–5 **(D)**, and L5–S1 **(E)** demonstrate the developmentally narrow central spinal canal with superimposed disc herniations at L4–5 and L5–S1. There is severe central spinal canal compromise at L4–5 and L5–S1. The L3–4 disc has a broad bulge without canal compromise. A 62-year-old male has classic symptoms of NIC; a sagittal T2 magnetic resonance image **(F)** demonstrates mild loss of disc space height and annular bulges at L2–3 and L3–4; the dominant element constricting the central spinal canal is the ligamentum flavum. Axial T2 images at L1–2 to L4–5 **(G, H, I, J**, respectively**)** confirm the severe central spinal canal compromise at L2–3 and L3–4 primarily because of ligamentum flavum thickening. A 68-year-old male has severe NIC with a walking tolerance of 10–20 m. A T2 sagittal image **(K)** shows severe stenosis at L4–5 and an L1–2 herniation. T1 unenhanced **(L)** and fat-saturated, T1-enhanced **(M)** images show intrathecal enhancement at L4–5 consistent with the breakdown of the blood–nerve barrier and Wallerian degeneration. Note also enhancing Modic I change and disc herniation at L1–2.

• Box 20.5 Lumbar Spinal Stenosis: Neurogenic Intermittent Claudication

- Decompression procedures for lumbar spinal stenosis are the most common spine surgery in the elderly.
- Neurogenic intermittent claudication (NIC) is a clinical syndrome; spinal stenosis is an anatomic observation.
- The best evidence of NIC pathophysiology suggests venous congestion from multiple sites of compression initiates an inflammatory reaction and Wallerian degeneration with blood-nerve barrier disruption and intraradicular edema.
- Clinically, multiple sites of compression at different segment levels or different spine compartments (central, lateral, foraminal) are necessary for NIC.
- Beware the specificity fault: The correlation between quantitative measures of the central spinal canal or dural sac size and patient symptoms or function is poor.
- Beware the sensitivity fault: Dynamic lesions, presenting only with extension and axial load, may make recumbent imaging insensitive.

the posterior columns and posterolateral tracts cephalad to the site of compression. Loss of anterior horn cells and corticospinal tract degeneration are visible at and caudal to the site of compression.

The developmentally narrow central spinal canal is a more universal substrate for CSM than is the case with NIC in the lumbar region. The sagittal diameter of the adult spinal cord is nearly constant, measuring about 8 mm from C3–C7; the normal cervical cord enlargement occurs primarily in the transverse plane.[278] The normal cervical spinal canal sagittal diameter (posterior vertebral body to spinolaminar line) is 17–18 mm (C3–C7) in a Caucasian population; these subjects rarely develop sufficient age-related change to provoke CSM. Edwards and LaRocca observed that patients with developmentally narrowed midcervical sagittal diameters of <10 mm were often myelopathic, patients with canals of 10–13 mm were at-risk for CSM, canals of 13–17 mm were noted in patients with symptomatic spondylosis but rarely myelopathy, and subjects with canals >17 mm were not prone to develop spondylosis.[280] Morishita studied the kinematics of subjects with congenitally narrowed canals; there is hypermobility in the lower cervical region, providing a biomechanical explanation for the significantly greater age-related change seen in this setting.[281] Hence, an individual with a congenitally narrowed canal is at-risk because of the limited space available for the cord and a greater propensity to age-related spondylotic change.

Acquired cervical central spinal canal stenosis encompasses age-related spondylotic change (most common), ossification of the posterior longitudinal ligament (OPLL), and OLF. Disc degradation results in a loss of disc space height, excess loading of the uncovertebral joints with osteophyte formation, excess facet loading causing hypertrophy, and central buckling of the ligamentum flavum. These processes circumferentially narrow the canal and directly compress the cord, exiting nerves and the anterior spinal artery. The most common levels of compromise were C3–4 (27%), C4–5 (37%), and C5–6 (29%) in a surgical series.[282] This series included patients with spondylosis only and those with OPLL. It is also known that the cross-sectional area of the cervical canal diminishes in both extension and flexion, with greater effects during extension.[47,48] Ventral compression of the cord compromises flow through the arterioles arising from the anterior spinal artery in the ventral sulcus of the cervical cord; dorsal compression reduces perfusion to the central gray matter. Oligodendrocytes are extremely sensitive to ischemic injury; resultant apoptotic cell death may cause the demyelination characteristically observed in CSM.[278] Animal evidence further supports the role of an inflammatory cascade in apoptotic cell death.[283]

Imaging

Historically, radiographic assessment of cervical anatomic stenosis relied on the AP dimension of the central spinal canal as measured from the posterior vertebral body to the spinolaminar line. The normal sagittal diameter from C3 through C7 is considered 17–18 mm. Edwards and LaRocca noted that a cervical canal with a sagittal diameter of less than 13 mm was at-risk for myelopathy; absolute stenosis was defined as being less than 10 mm.[280] The advent of cross-sectional imaging has allowed us to directly measure the diameters and cross-sectional areas of the cervical central spinal canal and the cervical cord. MRI has also given us the ability to evaluate physiologic parameters of the spinal cord: T2 hyperintensity, T1 hypointensity, gadolinium enhancement, and, with diffusion tensor imaging (DTI), fractional anisotropy (FA), and apparent diffusion coefficient (ADC).

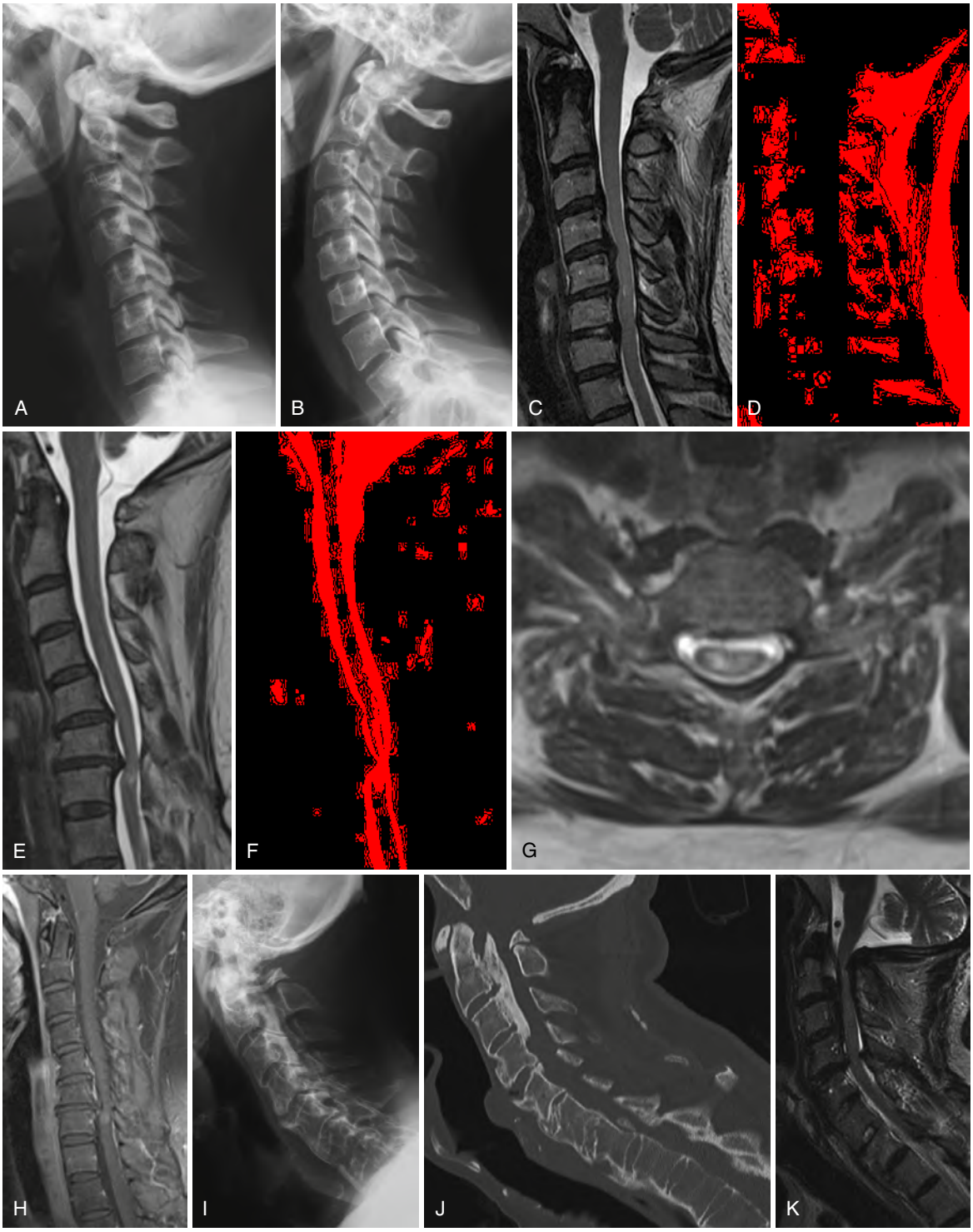
A 2010 study by Naganawa and associates demonstrated good intra- and interobserver reliability in the evaluation of the cross sections of the cervical canal and spinal cord with both CT/myelography and MRI.[284] They noted that dural sac diameter and cross-sectional area measurements were slightly but significantly larger with CT/myelography than fast spin-echo T2-weighted MRI; conversely, the diameters and cross-sectional areas of the spinal cord were slightly but significantly larger with MRI. MRI graded the stenosis as slightly but significantly more severe than CT/myelography. A 2009 study by Song and associates found no significant difference in interobserver or intra-observer reliability between CT/myelography and MRI.[285] With its superior spatial resolution, CT/myelography was somewhat better in assessing foraminal stenosis and much better in discriminating osseous versus soft tissue lesions. MRI was more reliable in identifying direct nerve root compression (Fig. 20.21).

Imaging Specificity

The significant prevalence of asymptomatic cervical central spinal canal stenosis was noted earlier in this chapter. When a population of patients with a clinical diagnosis of CSM is studied, the correlations appear more favorable. The transverse area of the spinal cord as measured by MRI correlates well with the severity of myelopathy and the pathologic changes observed in the cord in CSM.[286] The physiologic parameters of T2 hyperintensity or T1 hypointensity have provided further insight into the evolution of CSM. The several studies addressing these correlates are explored in a review.[287] From these studies, we can conclude the following:

1. Intramedullary T2 hyperintensity represents a range of reversible (edema) and irreversible (demyelination, gliosis, cystic necrosis) pathology.
2. Faint and indistinct T2 hyperintensity is more likely to reflect reversible edema.
3. Very intense and well defined T2 hyperintensity more likely represents fixed gliosis or cystic necrotic change.
4. Intramedullary T1 hypointensity represents irreversible necrosis and myelomalacia.

Gadolinium enhancement of the affected spinal cord in CSM was first reported in 2004.[288] A 2010 study by Ozawa[289] and a 2011 study by Cho[290] compared CSM patients who exhibited



• **Figure 20.21** Cervical central spinal canal compromise manifests as cervical spondylotic myelography (CSM). A 36-year-old female presents with very subtle bilateral hand incoordination, neck pain, and left arm symptoms. Her lateral radiograph **(A)** shows no lamina posterior to the articular pillar. Compare to a normal lateral radiograph **(B)**. Sagittal T2 **(C)** and T1 **(D)** images show effacement of cerebrospinal fluid and cord compression from the C4–C6 interspaces with subtle T2 hyperintensity in the cord at the C5–6 interspace level. Note that no dorsal epidural fat is visible above the C7–T1 level, a typical finding. A 48-year-old female had intractable upper extremity pain and dysesthesia involving the right lateral forearm. There were also long tract signs. Sagittal T2 **(E)** and T2 with fat saturation **(F)** demonstrate cord deformity at the C6–C7 interspace level, with focal T2 hyperintensity in the right side of the cord, as seen on the axial fast spine echo image **(G)**. Post-gadolinium sagittal T1-weighted image with fat saturation **(H)** shows enhancement at the site of T2 hyperintensity, a negative prognostic sign. A 77-year-old Caucasian male has slowly progressive myelopathy on clinical examination. Lateral radiograph **(I)** demonstrates ossification of the posterior longitudinal ligament in the upper cervical spine; note the coexistent manifestations of diffuse idiopathic skeletal hyperostosis. Computed tomography sagittal reconstruction **(J)** and sagittal T2 **(K)** images better depict the severe cord deformity at C2.

gadolinium enhancement with a non-enhancing control group. There was no correlation of enhancement with preoperative clinical symptoms. Enhancement disappeared in most patients within one year of surgical decompression; patients who exhibited preoperative enhancement had a poorer postoperative prognosis than those who did not. Of note, as further elucidated by other investigators, the cord enhancement in CSM often has a characteristic morphology.[291,292] On sagittal images, the enhancement typically appears as a narrow transverse band (pancake-like), located at or slightly caudal to the maximal level spinal stenosis. The degree of cross-sectional involvement of this intramedullary enhancement is variable on axial images, but it is commonly peripherally located and limited to the white matter, uni- or bilaterally. The abnormal cord T2 hyperintensity within which the enhancement occurs is typically much greater in longitudinal extent. The enhancement can persist for a variable duration after decompressive surgery. Awareness of the enhancement pattern can prevent diagnostic delay, expedite treatment, and avoid unnecessary biopsies.[291]

Floeth studied 20 CSM patients with FDG-PET in a single level stenosis setting at C3/C4 or C4/C5.[293] All the CSM patients showed a significant decrease in 18F-FDG uptake in the lower cord below the stenosis, relative to normal controls. A cohort of these patients also exhibited increased uptake at the level of stenosis. The patients with increased 18F-FDG uptake at the stenosis had a significantly shorter duration of symptoms, a more precipitous decline in function in the three months prior to decompression, and ultimately exhibited significant improvement after decompression. Patients without increased uptake at the stenotic zone did not recover neurologic function after decompression.

Early reports suggest that DTI may offer greater accuracy in the identification of symptomatic cord compromise than T2 hyperintensity or T1 hypointensity. The measured parameters are FA, mean diffusivity (MD), or ADC. The ADC or MD values reflect overall diffusivity in the tissue despite directional dependence. Anisotropy (directional dependence) of diffusion in white matter tracts results from oriented membrane structure (i.e. axons and myelin). Diminished FA values may reflect the loss of directionally oriented membrane structures, increased extracellular edema, or both. Several studies[287] suggest that diminished FA is more sensitive in the detection of early cord injury than intramedullary T2 hyperintensity and is better correlated with symptoms. This may help to select patients for surgical decompression, although additional work remains to be done. DTI has not been widely implemented in clinical practice for patients with CSM. The interested reader is referred to an excellent review on the role of DTI in the diagnosis and management of CSM.[294]

Imaging Correlates With Decompression Prognosis

The ultimate goal of imaging must be to improve the clinical outcomes of patients. In the CSM population, this currently implies the timely and appropriate selection of patients for therapeutic interventions, primarily surgical decompression. There is a large body of literature[287] that has examined the role of imaging in predicting clinical response to surgical decompression; imaging parameters under consideration include the cross-sectional area of the cord, intramedullary T2 hyperintensity, including its degree of intensity and multifocality, intramedullary T1 hypointensity, change or stability of intramedullary signal after decompression, recovery of cord cross-sectional area after decompression, and intramedullary gadolinium enhancement. These are summarized in Box 20.6. Utilization of these findings should assist in the selection and counseling of CSM patients regarding surgical decompression.

• Box 20.6 Cervical Spondylotic Myelopathy: Prognostic Factors for Surgical Decompression

1. Intramedullary T2 hyperintensity diminishes prognosis relative to the normal signal.
   a. Intense, focal T2 hyperintensity is a more negative prognostic sign than ill-defined hyperintensity.
   b. Multilevel T2 hyperintensity is a more negative prognostic sign than single level change.
   c. Resolution of T2 hyperintensity postoperatively improves prognosis.
   d. Expansion of T2 hyperintensity postoperatively diminishes prognosis.
2. Intramedullary T1 hypointensity greatly diminishes prognosis.
   a. Evolution of T1 hypointensity postoperatively diminishes prognosis.
3. Intramedullary gadolinium enhancement greatly diminishes prognosis.
4. Increased metabolic activity at the site of compression on 18F-fluorodeoxyglucose positron emission tomography improves prognosis over no increased activity.
5. Postoperative residual compression and failure of re-expansion of the cord cross-section are negative prognostic signs.

From Maus TP. Imaging of spinal stenosis: neurogenic intermittent claudication and cervical spondylotic myelopathy. *Radiol Clin North Am.* 2012;50:651–679.

Ossification of the Posterior Longitudinal Ligament

Ossification of the posterior longitudinal ligament (OPLL) is a multifactorial disease whose genetic basis is a defect in the nucleotide pyrophosphatase (NPPS) gene.[278] The prevalence is 1.9%–4.3% of the Japanese population and approximately 3% of the populations of Korea and Taiwan. It is implicated in up to 25% of North American and Japanese cases of CSM. It has a significant association (up to 50%) with DISH, and some consider it a subtype of DISH (Fig. 20.21). Like age-related causes of structural central spinal canal narrowing, it is often asymptomatic. The ossification is most common in the cervical region, where it causes static narrowing of the canal. The repeated impact of the ventral cord on the osseous mass contributes to myelopathic injury. Patients may present in their 40s and 50s with pain, chronic myelopathy, or acute neurologic injury after modest trauma. The natural history of ossification is progression. Close clinical follow up is warranted.

The ligamentous ossification may be identified on radiographs, CT, and MRI. On lateral radiographs, reduction of the sagittal canal diameter available for the cord by >60% correlates strongly with myelopathy.[293] The ossification is located from C2–4 in 70% of cases, T1–4 in 15%, and L1–3 in 15%.[295] On CT, the ossification may be classified as segmental (posterior to individual vertebrae, 39%), continuous (bridging across vertebra, 27%), mixed type (29%), and other (ossification posterior to discs, variable sagittal extension, 5%).[296] In addition to documenting the degree of central spinal canal compromise, the CT characteristics of OPLL can suggest dural penetration. CSF leaks are a significant risk in anterior decompression surgery, mainly when the dura is ossified or inseparable from the osseous ligamentous mass. On MRI, mature ligamentous ossification is of diminished signal intensity

on all sequences. Early OPLL may have an inhomogeneous signal and exhibit slight enhancement.[296] When mature, there is no enhancement, allowing differentiation from epidural fibrosis. The secondary signal alterations in the cord were described earlier in the chapter.

Systemic Disease Causal of Spine/Limb Pain

In the context of the very low prevalence of systemic disease as causal of spine or limb pain, this chapter has focused on the mechanical and inflammatory processes involving the articulations of the spine that most commonly provoke axial or radicular pain syndromes and syndromes of neurologic dysfunction. However, it must be remembered that detection of undiagnosed systemic disease—including stress fractures, infection, spondyloarthropathy, neoplasm, and dural fistula—is the primary role of spine imaging.

Stress Fractures

Stress fractures encompass fatigue fractures, in which normal osseous architecture is subjected to sustained supraphysiologic loads, and insufficiency fractures, in which deficient osseous structure fails under normal load conditions. Insufficiency (osteoporotic) fractures are the most common manifestation of systemic disease to present as back pain. In 2005, an estimated 2 million osteoporotic fractures occurred in the United States in patients aged >50 years; 27% were vertebral body fractures.[297] This is an underestimated prevalence, as many vertebral fractures remain asymptomatic. Each vertebral wedge configuration fracture accentuates load on the anterior aspect or adjacent vertebra and increases the annual risk of additional fractures five-fold.[298] Although many vertebral compression fractures are clinically important, it should be noted that a common, typically asymptomatic and clinically insignificant imaging observation is mild anterior wedging of the lower thoracic and/or upper lumbar vertebral bodies. This chronic appearance may sometimes be because of remote trauma, but it is probably most often simply a chronic developmental/physiologic finding. Aside from the emergent traumatic setting, in which CT reigns supreme, imaging of vertebral compression fractures begins with weight bearing radiographs, which provide a low cost means of assessing change over time with serial images but are relatively insensitive in fracture detection. Radiographic findings include a wedge deformity, most commonly of the superior endplate, which may be accompanied by increased density in the involved endplate in the acute or subacute phase. Chronic deformities often demonstrate remodeled osteophytes. MRI or bone scans are much more sensitive in fracture detection and can better assess acuity. The presence and extent of a marrow edema pattern (T1 hypointense, T2 hyperintense, most conspicuous on STIR or fat-saturated images) can provide an estimate of acuity. The signal abnormality in the marrow tends to be bandlike, paralleling the involved endplate; it may be traversed by a low signal line, adding further confidence to the diagnosis of fracture.

A primary role of imaging in this setting is the characterization of a vertebral fracture as benign or malignant. Carr and colleagues recently reviewed the differentiating imaging features of these two types of compression fractures.[299] Malignant lesions are much more likely to exhibit diminished T1 signal throughout the vertebral body, while benign lesions may demonstrate at least partial preservation of normal marrow signal. Extension of diminished T1 signal to the vertebral pedicles or posterior elements is relatively specific for malignancy. Discrete lesions in the bone, especially if destructive, are also strongly predictive of malignancy. A paravertebral or epidural non-hematomatous mass associated with a fracture is more common in and even more specific for malignant lesions but can also be seen in spinal infection. Posterior bowing (expansion) of the vertebral body strongly suggests malignancy. Gadolinium enhancement to a level greater than that noted in normal marrow suggests a malignant lesion. Associated disc rupture and retropulsion of the cortex without bowing of the posterior margin of the vertebral body suggest a benign lesion. Discrete linear zones of T2 hyperintensity similar to CSF adjacent to the fractured endplate (the fluid sign) are visible in 40% of osteoporotic compression fractures and are a finding of high specificity for a benign fracture.[300] Advanced MRI techniques, such as diffusion sequences or chemical shift imaging, may play a problem solving role.[299,301]

In the non-MRI compatible patient, CT can aid in the characterization of fractures but is less sensitive to marrow abnormality than MRI. Trabecular preservation within the vertebral body outside the fracture zone suggests a benign process. The ability of CT to display cortical or trabecular destruction or an adjacent soft tissue mass can aid in the diagnosis of a malignant or otherwise aggressive lesion. The fluid sign noted earlier is occasionally visible as a vacuum cleft containing gas under the fractured endplate, marking a benign osteoporotic compression. Bone scans are highly sensitive in fracture detection, but they are of poor specificity in characterization.

Pelvic insufficiency fractures are increasingly recognized as a cause of axial and somatic referred pain experienced in the low back, pelvis, groin, and proximal lower extremities. Postmenopausal osteoporosis is the dominant risk factor, along with pelvic radiation, corticosteroid use, rheumatoid arthritis, and osteomalacia. The role of osteoporosis is emphasized by the marked female predominance of these lesions, with a reported female-to-male ratio of 9:1.[302] Patients are typically in their sixth decade or older. There is often significant morbidity associated with insufficiency fractures. Taillandier and colleagues[302] noted that 50% of their patients did not recover their former level of independence, and in 25%, the insufficiency fracture precipitated institutionalization in their elderly study population. Sacral insufficiency fractures are the most common expression of this condition; pubic ramus fractures, parasymphyseal fractures, and para-acetabular fractures have also been described.

Lourie first described sacral insufficiency fractures in 1982.[303] Plain radiographs of the pelvis are relatively insensitive. The most common radiographic finding is a vertical sclerotic band in the sacral ala paralleling the SI joint, representing trabecular compression and callous formation.

Less commonly, one may see cortical disruption at the superior or inferior margins of the sacrum or directly visualize a fracture line. These are difficult findings to appreciate in the setting of osteoporotic bone and overlying bowel gas. In Grangier's[304] series, only 25% of patients had typical plain film findings. CT is more sensitive in detecting cortical disruption and the sclerotic margins of the fracture. Axial CT demonstrates the vertical component of the fracture. There is often a horizontal fracture line extending through the sacral body. This may be missed on axial images and better identified on coronal CT images. A vacuum phenomenon may also be observed within the fracture.

Technetium bone scan also represents a sensitive means of insufficiency fracture detection. The classic finding is the so-called Honda sign. Increased metabolic activity in bilateral vertical sacral

ala fracture lines are bridged by a horizontal line representing a fracture through the sacral body, resulting in a representation of the letter H. In Fujii's[305] series, 63% of patients with sacral insufficiency fractures exhibited this sign in toto, with 35% showing a variant thereof such as two vertical lines without a crossbar or a single vertical and horizontal line. The Honda sign taken with its variants had a 96% sensitivity and 92% PPV for sacral insufficiency fracture in this series.

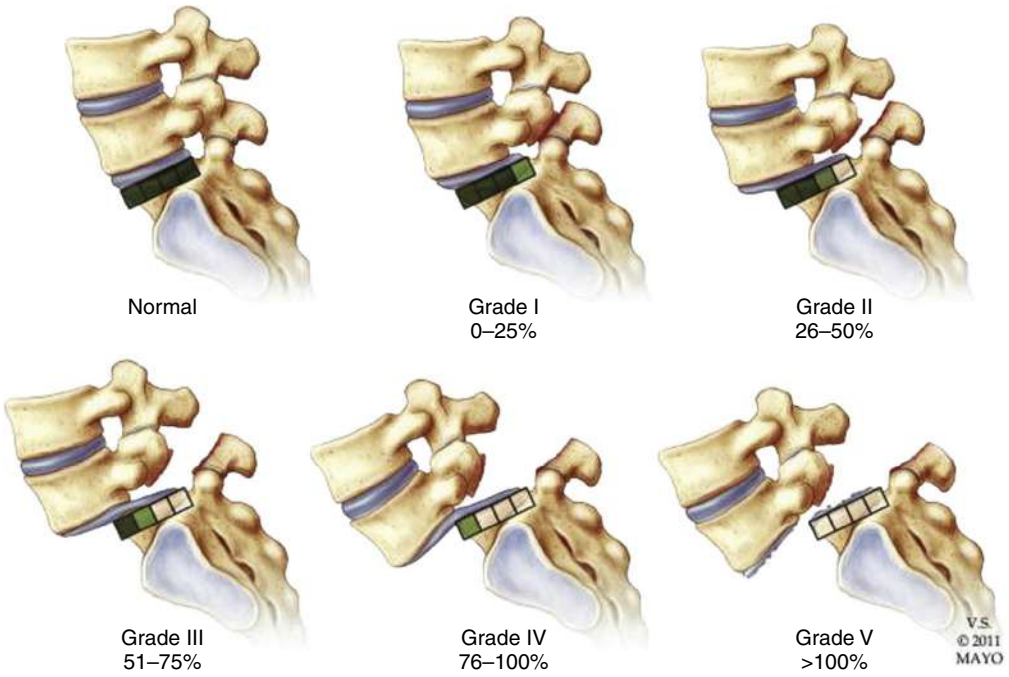
MRI is more sensitive than CT in the early detection of insufficiency fractures; it will reveal marrow edema (low T1, high T2 signal with gadolinium enhancement) in a pattern typical of insufficiency fracture (Honda sign) before sclerosis or a fracture line can be visualized with CT.[301] Imaging in the coronal plane is preferred; fat-saturated or STIR sequences are mandatory. In Grangier's series, marrow edema was observed in all cases as early as 18 days after symptom onset.[304] Over time, the fracture line will become visible within the zone of marrow edema as a line of diminished signal. Fluid (very high, homogeneous T2 and corresponding low T1 signal) may be detected within insufficiency fractures. The confidence in the diagnosis of sacral insufficiency fracture will be increased by the presence of similar bone lesions in the pubic rami, immediately about the pubic symphysis, and in the para-acetabular region, also typical sites of insufficiency fracture.

Spondylolysis

Spondylolysis, or isthmic spondylolisthesis, describes a defect in the pars interarticularis, which may be unilateral or bilateral. It is considered a fatigue fracture occurring within a vulnerable pars. The vulnerability may be related to the distribution of ossification centers within the posterior neural arch, not a deficit in bone quality. Spondylolysis has a familial predisposition. There is a 2–4:1 male-to-female predominance. The incidence of spondylolysis has been estimated at 7% in the United States population.[306] Spondylolysis is frequently asymptomatic, but it is a particular clinical issue in adolescent athletes. A retrospective study of lumbar radiographs in over 4000 athletes demonstrated a 13.9% rate of spondylolysis with concomitant spondylolisthesis in 47%.[306] Spondylolysis occurs most commonly at the L5 level (67%), followed by the L4 (15%–20%) and L3 levels (1%–2%). It is unusual in the cervical region, where it most often occurs at the C6 level. Spondylolysis is extremely rare in the infant population but appears to develop in childhood or adolescence, with no significant change in its incidence beyond age 20.

Although considered a fatigue fracture, it is unusual in that there is seldom an effective healing response, and the osseous defect is persistent. The pars defect is frequently a synovial-lined pseudoarthrosis. Shipley demonstrated that injection of the facet immediately superior to a pars defect showed communication with the pars defect cavity in 30 of 32 facets, with communication to the next most inferior facet in 20 of 32 facets.[307] The presence of synovial fluid in the defect likely contributes to its diminished capacity to heal.

Radiographic findings of spondylolysis are often evident on lateral plain films where a radiolucent band can be directly visualized across the pars interarticularis, with or without a sclerotic margin; there is no role for oblique radiographs. Spondylolisthesis refers to the anterior translation of the vertebral body bearing the spondylolytic defects in relation to the vertebral body below (Fig. 20.22). Spondylolisthesis is graded from I to V based on the percentage of anterior translation relative to the AP dimension of the vertebrae: grade I, 0%–25%; grade II, 26%–50%; grade III, 51%–75%; grade IV, 76%–100%; and grade V, >100% (spondyloptosis).[301] Most cases of spondylolisthesis are of grade I. A trapezoidal appearance of L5 with a dome-shaped superior endplate of S1 can be observed in chronic spondylolysis with spondylolisthesis.



• **Figure 20.22** Spondylolisthesis, modified Meyerding classification. Modified Meyerding classification of spondylolisthesis: grade I, 0%–25%; grade II, 26%–50%; grade III, 51%–75%; grade IV, 76%–100%; grade V, greater than 100% (spondyloptosis [falling off]). (From Murthy NS. Imaging of stress fractures of the spine. *Radiol Clin North Am.* 2012;50:799–821.)

CT allows direct visualization of the pars defect interposed between the adjacent facet joints on axial images. Sagittal reconstructions make the defect more obvious. Care must be taken to distinguish between a true pars defect and severe facet arthrosis. CT will also help distinguish between a stress response (sclerosis, hypertrophy) in the contralateral pedicle or pars in a unilateral spondylolysis and an osteoid osteoma. CT allows characterization of the process as a stress response (sclerosis), an incomplete fracture, or a completed fracture. Fujii and colleagues categorized these types as early, progressive, and terminal.[308] The early stage consists of a narrow fissure with sharp margins; the progressive stage consists of a narrow fissure with less well defined, rounder margins; and the terminal stage consists of a wide defect with rounded, sclerotic margins. Early stage lesions healed with conservative care, including bracing, more frequently than progressive lesions; no terminal stage lesions healed (see Fig. 20.23).[308]

The defect in the pars interarticularis can be directly visualized on multiplanar MR imaging, especially if thin sections and specific oblique axial plane images are acquired.[309,310] A systematic review by Dhouib and colleagues concluded that MR imaging has high diagnostic performance for detecting pars defects in young adults and that it can be considered a first line imaging test since it avoids exposure to ionizing radiation unlike radiographs, CTs, and bone scans.[311] Several ancillary signs have been described on MRI, including (1) an increase in the sagittal diameter of the central spinal canal at the level of the pars defect, (2) reactive marrow changes (hypointense T1, hyperintense T2) within the adjacent pedicle, and (3) wedging of the posterior aspect of the associated vertebral body, usually L5.[312] Reactive marrow changes in a vertebral pedicle are not specific for the presence of spondylolysis and may be observed in the presence of adjacent facet arthrosis or synovitis. Hollenberg and colleagues developed an MRI classification of spondylolysis (Table 20.5).[313] A subsequent study comparing CT staging and MRI findings noted that CT-defined early stage lesions all exhibited T2 hyperintensity in the ipsilateral pedicle; terminal stage lesions never exhibited T2 hyperintensity in the pedicle.[313] Nearly 80% of lesions with T2 hyperintensity in the pedicle healed with conservative care.[314]

TABLE 20.5 MRI Classification of Spondylolysis

Grade	Description	MRI Features
0	Normal	Normal bone marrow signal No cortical disruption
1	Stress reaction	Bone marrow edema No cortical disruption
2	Incomplete fracture	Bone marrow edema Incomplete fracture through the pars interarticularis
3	Acute complete	Bone marrow edema Complete fracture through the pars interarticularis
4	Chronic complete	No bone marrow edema Complete fracture through the pars interarticularis

From Murthy NS. Imaging of stress fractures of the spine. *Radiol Clin North Am.* 2012;50: 799–821, Table 1.

MRI, Magnetic resonance imaging.

Spondylolysis has also been assessed with SPECT/CT, although at the cost of radiation dose to a typically young population. Gregory and colleagues assessed the diagnostic value of combining SPECT with CT in the evaluation of spondylolysis.[315] They described four categories of patients: group A: (+) SPECT and (+) CT findings for spondylolysis; group B: (+) SPECT and (–) CT findings for spondylolysis +/– sclerosis of the pars; group C: (–) SPECT and (+) CT findings for spondylolysis; and group D: (–) SPECT and (–) CT findings for spondylolysis. Group A and B patients were felt to have a healing potential with early fatigue fractures or stress responses; group C patients had terminal lesions without healing potential, and group D patients had other pain generators, often the disc.[315] Although adult spondylolysis is often asymptomatic, there is a tendency to develop significant disc failure at the level of the pars defect, which may cause late progression of the degree of vertebral displacement (spondylolisthesis) and associated neural element compromise resulting from foraminal stenosis, which is well demonstrated on sagittal MRI. Spondylolysis patients may then experience axial pain caused by the inflammatory change about the pars defect, discogenic pain from the failed disc, and radicular pain from secondary foraminal compromise.

Characterization of pars defects sufficient for therapeutic planning requires assessment of both morphologic and physiologic parameters. A stress response in the pars or an incomplete fracture may respond to conservative therapy with healing; completed chronic fractures seldom heal and are often asymptomatic. Persistent symptoms in the face of a chronic completed fracture may reflect secondary phenomena of discogenic pain or radicular pain from foraminal stenosis. The combined morphologic and physiologic characterization can be performed with SPECT/CT or MRI. The interested reader is referred to a far more complete review by Murthy.[301]

Spine Infection

Extradural spinal infections are primarily the result of arterial seeding. In children, the disc and endplate have a rich blood supply; infection occurs initially in the disc itself. In adults, the disc is avascular; an infection develops in the anterior subchondral vertebral body with secondary spread to the disc, adjacent vertebrae, and subligamentous (deep to the anterior longitudinal ligament) space. Most disc space infections involve two adjacent lumbar vertebrae. Spread from contiguous infection or direct disc inoculation (surgery, injections, discography) is much less common.

Pyogenic disc space infection involves men much more commonly than women (2–3:1) in the fifth to seventh decades of life.[316] Infection is usually unimicrobial, *Staphylococcus aureus* is the most common pathogen, and urinary tract infections are the most common source of seeding.[317] Clinical symptoms may precede radiographic findings by 1–8 weeks. Clinical signs of elevated erythrocyte sedimentation rate, white blood cell count, and C-reactive protein are usually present. The C-reactive protein and erythrocyte sedimentation rate are both sensitive but not specific, while generally, the white blood cell count is the least helpful inflammatory marker. Plain films may reveal early rarefaction of anterior subchondral bone, followed by a loss of disc space height (at 1–3 weeks) with subsequent destructive changes in the vertebral endplates. Late changes include variable amounts of sclerosis, kyphotic deformity from vertebral collapse, and ankylosis. CT in pyogenic discitis shows early hypodensity in the disc, moth-eaten destruction of the vertebral endplates, and inflammatory changes and/or a mass in the paravertebral soft tissues and/or epidural space. Scattered gas formation may be observed. Extensive gas formation in the central

portion of the disc is typical of noninfectious disc degeneration. The disappearance of such a vacuum disc sign may herald infection. This is particularly true if there are associated endplate erosive changes, even if subtle. Note that the disappearance of vacuum phenomenon (as best seen on CT) may also occur in uninfected discs because of replacement by fluid (as best seen on MRI), which is likely a dynamic, time- and position-dependent process.[318]

MRI is the preferred imaging modality for the evaluation of discitis, with a greater than 90% sensitivity and specificity in disease detection.[316,317] It also provides critical anatomic information. Early marrow changes are elevated T2 signal (best observed with fat saturation or STIR), diminished T1 signal, and gadolinium enhancement (Fig. 20.24). There is a loss of the crisp dark cortical line of the vertebral endplate. The intranuclear cleft is lost within

• **Figure 20.23** Stress fractures, including spondylolysis. Spondylolysis at L5 is visible on flexion **(A)** and extension **(B)** radiographs. Although there is no translation of L5 on S1, the degree of rotation (12 degrees) qualifies this as unstable. In unilateral spondylolysis, the contralateral pars often show hypertrophy and sclerosis **(C)**. Computed tomograph (CT) can be used to stage pars fractures as early stage **(D)** with a narrow, sharply marginated fissure; progressive stage **(E)** with a narrow fissure having slightly rounded margins; and terminal stage **(F)** with a wide fissure with rounded margins and sclerosis. Typical sacral stress fracture *(arrows)* demonstrates a low signal fracture line on a coronal T1 image **(G)**, a linear zone of T2 hyperintensity on a STIR image **(H)**, whereas CT demonstrates a linear zone of sclerosis **(I)**. The integrity of the neural foramina is better defined on CT. (From Murthy NS. Imaging of stress fractures of the spine. *Radiol Clin North Am.* 2012;50:799–821.)

the disc, and foci of elevated T2 signal and gadolinium enhancement develop. The paravertebral and epidural soft tissues show diffuse enhancement (phlegmon) or frank abscess formation, with zones of hypo-enhancement and increased T2 signal where liquid purulent material is present, surrounded by peripheral enhancement. The imaging differential diagnosis consists of a Modic type I degenerative change, atypical cartilaginous (Schmorl's) nodes, adjacent metastatic lesions, osteomalacia secondary to osteodystrophy, and pseudoarthroses in patients with AS or a Charcot spine. Discrimination from a Modic type I endplate change can be particularly vexing; differential points are presented in Table 20.6. Although not as commonly applied in spinal imaging as in the brain, diffusion-weighted imaging (DWI) can be helpful when attempting to distinguish infectious spondylodiscitis from Modic type I endplate changes. Patel and colleagues demonstrated that the presence of a "claw" sign on DWI strongly suggests Modic I, while its absence strongly suggests infection.[319] This sign refers to "well-marginated, linear, typically paired regions of high signal situated within the adjoining vertebral bodies at the boundaries between the normal bone marrow and vascularized bone marrow that lies close to the affected disc."[319] An additional helpful discriminating feature for lumbar spinal infection is the "imaging psoas" sign.[320] This sign refers to T2 hyperintensity in the psoas musculature, which in a study of 51 biopsy-proven or clinically diagnosed patients with osteomyelitis-discitis compared to 50 age-matched control patients was highly correlated with spinal infection (sensitivity and specificity were both 92%). Despite these additional and more conventional imaging findings, imaging cannot always confidently diagnose spinal infection versus sterile inflammatory changes. In challenging cases, image guided biopsy and culture are appropriate.

MRI abnormalities lag behind the clinical syndrome. Imaging may be minimally abnormal early in the disease process but then remain quite dramatic even after a gratifying clinical response to antibiotics. Following the short term efficacy of antibiotic therapy, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white cell count will be more useful than repeated imaging. Follow up imaging should be reserved for patients with a clinical concern for continued infection with central spinal canal compromise. Persistently elevated or increasing ESR or CRP at week 4 of antibiotic therapy predicts treatment failure.[321]

Nuclear medicine scans using gallium-67 citrate and technetium-99m diphosphonate are complementary in the evaluation for suspected spondylodiscitis. A series by Hadjipavlou and colleagues demonstrated 100% sensitivity, specificity, and accuracy for the combination of gallium and technetium scans when compared with surgical biopsy results.[322] Gallium may be helpful in following the resolution of the infection. All nuclear medicine techniques lack anatomic information; they cannot define the extent of epidural or paraspinal disease or central spinal canal compromise.

Pyogenic epidural abscesses may arise from the contiguous spread of adjacent spondylodiscitis or facet joint infection, but they are most commonly primary because of the hematogenous dissemination or direct inoculation of the epidural space. *S. aureus* is the most common pathogen; immune compromise, especially diabetes, is common.[316] Emergent MRI is the imaging modality of choice. This will demonstrate a T1 hypointense, T2 hyperintense epidural process with peripheral or heterogenous enhancement, depending on the physical state of abscess versus phlegmon. The midline ventral epidural septum may be violated; most neoplasms respect this structure. Compression of the dural sac is common;

TABLE 20.6 Differentiating Spondylodiscitis From Modic Type I Endplate Changes

	Favoring Spondylodiscitis	Favoring Modic Type I Endplate Changes	Pitfall/Comments
Disc Space Signal	T2 hyperintensity	T2 hypointensity or lack of T2 hyperintensity	Severely degenerated discs rarely can be T2 hyperintense (even fluid signal)
Disc Space Enhancement	Present	Absent	Rarely absent in infection; rarely present in Modic I
Disc Space Vacuum Sign	Absent, or only scattered	Often present; a large amount of confluent gas on radiographs virtually exclude infection	Gas may be present early in infection, in rare gas-forming bacterial infections, or in rare fistulas with the gastrointestinal tract
Vertebral Body Endplates	Endplate destruction	Lack of endplate destruction	Modic I can have endplate irregularity; *computed tomography is very useful here*
Paraspinal, Epidural Spaces	Inflammation or abscess	Absent	Peripherally enhancing disc herniation can be confused for abscess
Location	Anteriorly eccentric	Laterally eccentric: at point of biomechanical stress (e.g. inner aspect of the curve)	Both spondylodiscitis and Modic I are often along the entire endplate
Fever, Elevated Inflammatory Markers	Present	Absent	Fever is only variably present in spondylodiscitis; inflammatory markers are nonspecific
Short Term Follow Up	Progression	Stability	If *remote* comparison images are available, even Modic I can show significant progression

From Diehn FE. Imaging of spine infection. *Radiol Clin North Am.* 2012;50:777–798.

severe compromise with neurologic deficit precipitates emergent decompression. Imaging resolution of an epidural abscess more closely parallels the clinical state than in spondylodiscitis. Spinal subdural abscesses are less common but can be very long segments and also constitute an emergency.

Pyogenic facet joint infection is uncommon; it usually results from hematogenous dissemination, although direct inoculation caused by invasive procedures is reported. Clinical presentation may resemble spondylodiscitis, although most commonly with lateralizing symptoms; the lumbar spine segment is most frequently affected. Bilateral involvement may occur via the space of Okada.[193] CT will demonstrate an erosive process centered on the joint with inflammatory change in the adjacent multifidus muscle. MRI will demonstrate marrow edema in the articular processes, a joint effusion, and edematous changes in the multifidus; enhancement in the joint with peripheral enhancement about an adjacent paraspinal or epidural abscess or uniform heterogeneous enhancement within a phlegmon may be noted.

Tuberculosis (TB) remains the most common cause of spinal infection worldwide, and it is of increasing incidence in industrialized societies. Clinical symptoms are usually insidious. Whereas 90%–100% of patients will have back pain, only 50% will have constitutional symptoms or fever. Tuberculous spondylitis (Pott's disease) arises from hematogenous (arterial) spread of tuberculous bacilli, usually from a pulmonary source. This initially lodges in the anterior subchondral bone. There is early anterior subligamentous extension and then spread to adjacent vertebrae, often multiple, as well as spread across the disc. Neurologic deficit occurs in a moderate number of patients because of epidural extension. Posterior elements tend to be spared. Extensive anterior column destruction with gibbus deformity is characteristic.

Tuberculous spondylitis with discitis shows disc space narrowing, vertebral osteolysis with collapse, and gibbus deformity on plain films. The thoracolumbar junction is most frequently affected, with less frequent involvement as one ascends the thoracic or descends the lumbar spine.[316] Plain films may not be abnormal until two to five months after the onset of infection. Paraspinal soft tissue masses caused by subligamentous spread, particularly with calcification, are characteristic. CT will demonstrate the osteolytic changes of spinal tuberculosis earlier than plain films will. It more readily demonstrates epidural involvement, particularly when calcification or bone fragments are visible in the epidural space. Paraspinal involvement is also well demonstrated.

MRI is the primary imaging procedure for the detection of spinal TB. Early changes of tuberculous spondylitis with discitis are very similar to pyogenic disc space infection, with marrow and disc inflammatory changes consisting of elevated T2 signal, diminished T1 signal, and enhancement. Extensive subligamentous spread of disease suggests TB, especially when the disc spaces are relatively spared. Paraspinal abscesses, granulomas, and epidural involvement are common. Epidural involvement may be observed in 60%–80% of cases.[316] A potential differentiating feature favoring tuberculous over pyogenic spondylitis when the ventral epidural space is affected in the perseveration of the midline central septum (anterior meningovertebral ligament).[323] When preserved, the tuberculous lesion in the ventral epidural spaces takes on the configuration of a draped curtain.[323] In contrast to indolent infection or neoplasm, more rapidly aggressive epidural disease processes, such as pyogenic epidural infection (phlegmon, abscess) or hematoma, tend to lack this draped curtain sign this sign because of violation of the midline ligament.[324]A second pattern of tuberculous infection is spondylitis without discitis (see Fig. 20.24).[325] This describes lytic lesions in the central portions of the vertebral bodies, often multiple, without disc involvement. This pattern of involvement was present in approximately 50% of patients in one large series.[322] Imaging findings consist of discrete, destructive vertebral body lesions. Plain films show well defined lytic lesions, often multifocal, and with more frequent posterior element and cervical involvement than is observed in tuberculous discitis. Lytic lesions may exhibit marginal sclerosis on CT, indicating a more indolent lesion than a typical metastatic deposit. These lesions typically enhance peripherally on MRI, often with a cystic central cavity. There may be cortical destruction with an adjacent paravertebral abscess. Because of the greater frequency of multiple lesions, this entity must be distinguished from metastasis, myeloma, or lymphoma.

MRI has significantly advanced the diagnosis of spinal infection, allowing this to be suggested as a likely diagnosis before destructive changes have evolved. However, the MRI findings remain unspecific, and accurate diagnosis and therapy require tissue sampling for histology and culture. Image guided percutaneous aspiration/biopsy with large caliber bone cutting needles can provide minimally invasive tissue sampling. However, the yield of this procedure is relatively low, especially, but not only, in patients in whom antibiotics have been initiated.[326]

Inflammatory Spondyloarthropathy

Noninfectious inflammatory disease of the spine includes rheumatoid arthritis (RA) and the seronegative spondyloarthropathies (SpA), of which AS is the prototype. These diverse entities have spine involvement in common and may present with axial spine pain.

Rheumatoid arthritis is most common in the cervical spine, sometimes called the fifth limb in RA patients. Symptoms and signs of cervical spine involvement are present in 60%–80% of RA patients.[327] Spinal involvement by RA is unlikely in the absence of hand involvement. The most frequent site of involvement is the atlanto-axial articulation. Inflammatory pannus may be seen on MRI as a low T1, high T2 signal-enhancing mass posterior to the dens. This may cause compression of the cervicomedullary junction. The inflammatory change may destroy the transverse and alar ligaments, resulting in atlanto-axial instability in 20%–25% of RA patients. A distance of greater than 4 mm between the posterior arch of C1 and the cortical surface of the dens on radiographs is abnormal and is most evident in flexion views. The destruction of supporting structures at the craniocervical junction may also result in cranial settling, vertical migration of the dens into the foramen magnum, with possible compression of the C1 and C2 cranial nerves, the medulla, and vertebral arteries.

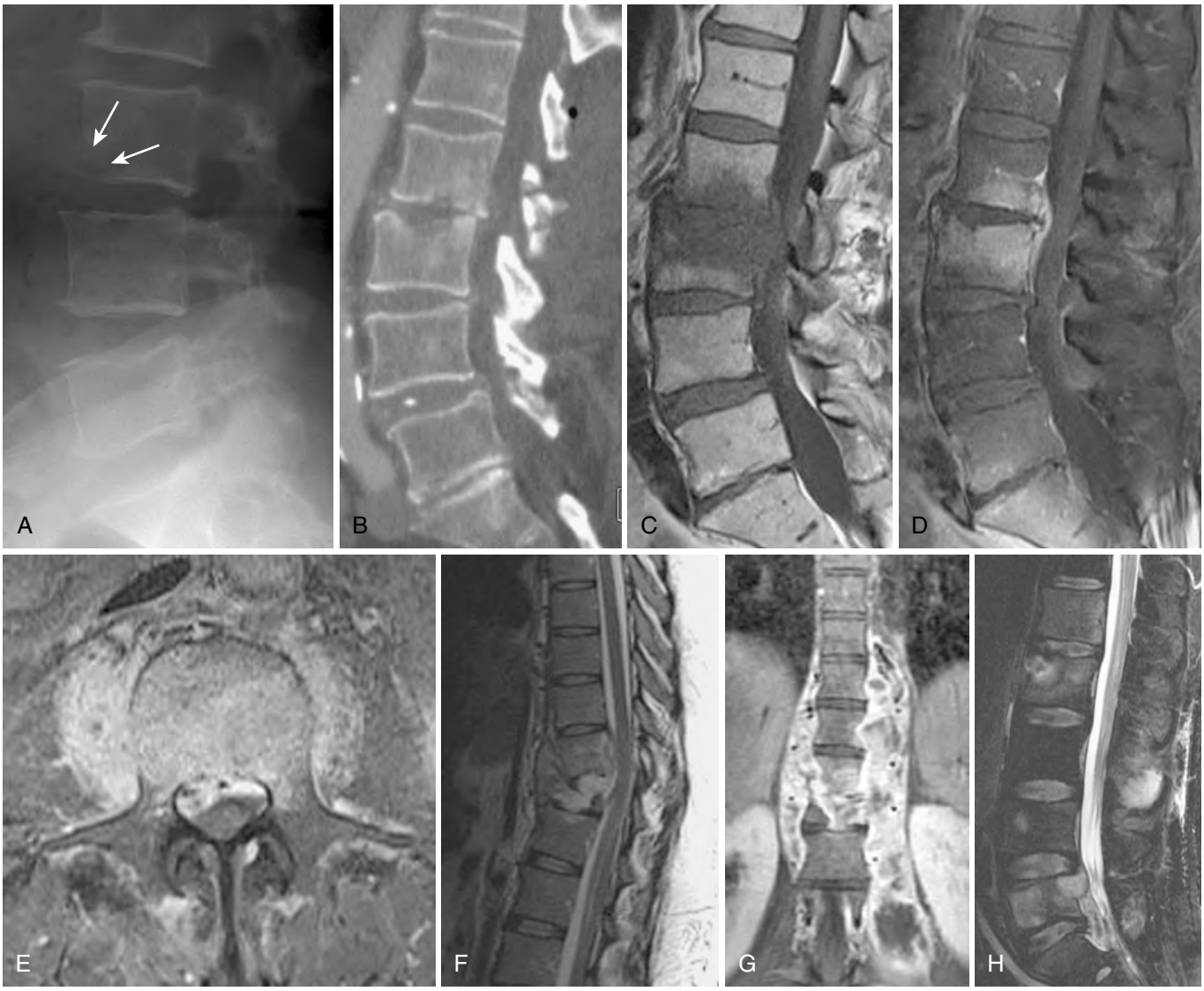
The cervical spine below the C1–2 articulations demonstrates erosive arthritis in the uncovertebral and facet joints in RA patients. The inflammatory change can be demonstrated on MRI as increased T2 signal on STIR sequences and gadolinium enhancement on fat-saturated T1 sequences. This results in multilevel instability, with anterior subluxation of successive vertebral bodies in flexion, the so-called step ladder cervical spine, noted in up to 30% of RA patients.[327] Disc space narrowing and endplate sclerosis are common, but this may be a secondary phenomenon to the posterior element instability.

Involvement of the thoracic and lumbar spine in RA is uncommon. Synovitis and erosive change may be present in the facet and costovertebral joints, but these findings are inconstant and not well demonstrated. Discovertebral changes may be present, but it is again unclear if these are primary inflammatory lesions

or a response to facet instability. The sacroiliac joints may show inflammatory change but with much less frequency and severity than in AS patients.

The seronegative spondyloarthropathies are a group of rheumatoid factor negative inflammatory disease processes affecting the spine and sacroiliac joints, with a unique predilection for entheses. Historically these have included AS, psoriatic arthritis, reactive arthritis (formerly known as Reiter's syndrome), and arthritis associated with inflammatory bowel disease. The categorization of these diseases has evolved, most recently in 2009, with the designation of axial spondylarthritis for the spectrum of disease with axial, as opposed to peripheral, dominance.[328] Axial spondylarthritis requires active sacroiliitis on MRI plus one or more features of spondylarthritis or human leukocyte antigen B27 (HLA-B27) positivity with two or more features of spondylarthritis. This discussion only encompasses the axial imaging features of the classically defined processes (Fig. 20.25).

MRI is the necessary imaging modality for the assessment of disease activity in the SI joints and spine articulations. MRI or CT can demonstrate the aftermath of disease: joint space narrowing, subchondral erosions, reactive sclerosis, or periarticular fat deposition (a Modic II analog); only MRI can assess active inflammation with T2 hyperintensity (STIR or fat-saturated images) and gadolinium enhancement on fat-saturated T1 images.



• **Figure 20.24** Spondylodiscitis. A lateral radiograph **(A)** demonstrates early pyogenic spondylodiscitis manifest as subtle destruction of the anterior inferior aspect of the L3 vertebrae (*arrows*). In another patient, a sagittal computed tomography reconstruction **(B)**, sagittal T1-unenhanced **(C)** and enhanced **(D)** and axial T1-enhanced magnetic resonance images (MRIs) **(E)** of a patient with L2–3 pyogenic discitis. Note the loss of disc space height, endplate destruction, low T1 signal, and extensive vertebral, epidural, and paraspinal enhancement. Sagittal T2-weighted MRI **(F)** of a back pain patient without myelopathy demonstrates vertebral destruction with kyphotic deformity; this is tuberculous spondylodiscitis. Coronal T1-enhanced MRI **(G)** in the same patient demonstrates the extensive paraspinal disease typical of Pott's disease. A sagittal T2-weighted MRI **(H)** in another patient with tuberculous spondylodiscitis; note the multiple vertebral lesions with sparing of the discs. This can be confused with metastatic disease. Tissue sampling is essential. (From Maus T. Imaging the back pain patient. *Phys Med Rehabil Clin N Am*. 2010;21:725–766.)

AS is the prototypical seronegative spondyloarthropathy; active disease in the SI joints by MRI criteria is integral to its diagnosis. AS has a prevalence of up to 0.1% in the general population; a very high percentage will be HLA-B27 positive. Males dominate by a ratio of 4:1. The disease involves synovial and cartilaginous joints and entheses (ligament and tendon insertions on the bone) with a strong predilection for the axial skeleton. The most common presentation is low back pain with inflammatory features (Calin criteria, four out of five of insidious onset, age <40 years, three months persistence, morning stiffness, and pain improved by exercise).[329] Radiating pain mimicking sciatica may be observed in up to 50% of patients.

Imaging findings in AS include sacroiliitis, ultimately bilaterally symmetric, and multiple manifestations of spondylitis (see Fig. 20.25). Sacroiliitis is the uniform initial imaging finding. Early plain film findings of sacroiliitis are blurring of the subchondral cortex by small erosions, predominantly on the iliac side of the joint. As the erosions coalesce, the joint space appears widened and ill-defined; sclerotic reaction develops in the trabecular bone about both sides of the joint. Over time the joint undergoes ankylosis via direct osseous bridging; the joint space is no longer visible, and the sclerosis resolves.[330] MRI can detect inflammation in the SI joint in symptomatic patients with normal plain films. Inflammation can be reliably identified with low interobserver variability as high T2 signal on STIR sequences or gadolinium enhancement on fat-saturated T1 images.[331] In patients with recent onset axial low back pain with inflammatory clinical characteristics, SI joint inflammation may be detected by MRI in one-third of patients and structural changes in one-sixth of patients.[331] Inflammation is initially observed in the iliac side of the joint at its caudal and dorsal aspects, and in the adjacent dorsal entheses.

Spine findings in AS are present in 50% of patients and include osteitis, syndesmophyte formation, discovertebral lesions, and inflammation leading to ankylosis of facet and costovertebral joints.[330] Osteitis is observed at the anterior margins of the discovertebral junction, termed the "Romanus lesion." On plain films, sclerosis at these sites leads to increased density of the anterior corners of the vertebra, termed the "shiny corners sign."[330] Remodeling of the anterior margin of the vertebral body as a result of osteitis straightens the normally concave anterior vertebral margin, referred to as "squaring" of the vertebra. These findings are most evident in the lumbar region. MRI is more sensitive to the early detection of osteitis, recognized as diminished T1 and increased T2 signal and enhancement at the anterior vertebral corners.[330] Osteitis at the margins of the discovertebral junctions leads to reactive bone formation in the outer annulus fibrosis, which ultimately bridges the margins of adjacent vertebrae. These vertically oriented osseous struts are syndesmophytes. They are distinguished from osteophytes by their vertical orientation and gracile nature; osteophytes are oriented in the horizontal plane and are bulkier. Syndesmophytes are most common at the anterior and lateral aspects of the vertebral body; when long standing, the ossification may involve the anterior longitudinal ligament.

Erosions at the discovertebral junction are termed "Andersson lesions"; this inflammatory destruction of the vertebral endplate with intravertebral disc displacement can progress to pseudarthrosis. The imaging findings can be challenging to differentiate from those of infectious spondylodiscitis. Endplate destruction is visible on plain films; MRI demonstrates structural and inflammatory change. The inflammatory change will undergo evolution reminiscent of the progression from Modic type 1 to Modic type 2. Over time, sclerosis and transdiscal ossification are leading to ankylosis. The facet and costovertebral joints show similar findings, with initial periarticular erosions followed by sclerosis and ankylosis. Enthesitis of the posterior interspinous and supraspinous ligament attachments ultimately leads to ossification of these structures, visible as a vertical midline osseous band on frontal radiographs, the so-called dagger sign. The most common inflammatory spinal lesions in the midthoracic spine (T7–T8) and the midlumbar region (L2–3).

AS may also produce changes at the atlanto-axial articulation. Synovitis may cause erosive changes in the dens, although the extent of inflammatory change seldom reaches that noted in RA. Atlanto-axial subluxation may be present. The extensive ankylosis observed in patients with long standing AS leads to flattening of the lumbar lordosis and exaggeration of the thoracic kyphosis. The rigidity places these patients at-risk for catastrophic fracture-dislocations with modest trauma, most commonly with a hyperextension mechanism. The cervical spine is most frequently involved; neurologic deficits are common. Plain film evaluation is difficult because of the osteopenia typical of these patients; the three-column nature of these fractures is best appreciated with CT or MRI. The threshold for the use of advanced imaging in the AS patient with trauma should be low. Three-column fractures that do not cause acute neurologic injury or go undetected may be a cause of chronic focal pain as pseudarthrosis. MRI will show a linear zone of inflammatory change, often through a disc space with extension through the posterior elements. The cortical disruption may be best appreciated on CT. Finally, some AS patients will have findings of dural ectasia (see Fig. 20.25). The thecal sac will be abnormally capacious with diverticular-like outpouchings; there is associated osseous erosion in the posterior elements, medial margins of the pedicles, and the posterior vertebral body. These patients may present with a cauda equina syndrome, perhaps related to arachnoiditis.

Psoriatic arthritis (PA) is far less common than AS, affecting approximately 7% of patients with cutaneous psoriasis.[330] Approximately 10%–25% of patients with moderate to severe skin disease will have abnormal SI joint radiographs. Spondylitis is present in a roughly similar proportion but may or may not coexist with sacroiliitis. Males and females are equally affected.[330] The sacroiliitis is usually bilateral but asymmetric, with a lesser tendency to progress to osseous ankylosis. Erosions and foci of reactive sclerosis tend to be larger and more discrete than in AS. The spondylitis in PA is characterized by asymmetric, coarse paravertebral ossification, more strongly resembling osteophytes than syndesmophytes. Vertebral squaring and shiny corners are absent. Facet involvement is infrequent.

Reactive spondylarthritis (RS) describes an inflammatory arthropathy, preferentially affecting the heel and large peripheral joints.[330] Sacroiliitis is very common, affecting up to 45% of patients. It is more commonly unilateral or asymmetric than in AS; ankylosis is rare. Spine involvement may be identical to that of PA but more common; the lumbar spine is involved in 30% of RS patients.[330] In the setting of a triggering infection (often chlamydia) and the triad of urethritis, uveitis, and arthritis, the term "Reiter's syndrome" may be applied.

Enteropathic arthritis may also be observed in association with ulcerative colitis or Crohn's disease. The initial presentation of back pain may precede symptoms of gastrointestinal disease. The spondylitis and sacroiliitis noted in association with these conditions are indistinguishable from classic AS. Sacroiliitis is usually bilaterally symmetric, progressing to ankylosis. Spondylitic findings of vertebral squaring, discovertebral lesions, syndesmophytes, and involvement of the facet joints are typical.

Spine Neoplasm

Spinal neoplasms are classified by the anatomic compartment from which they arise: extradural, intradural-extramedullary, or intramedullary. Extradural neoplasms arise from the vertebral bodies, within the paravertebral soft tissues, or within the epidural space. These include metastatic lesions, hematologic malignancies, and primary osseous or cartilaginous tumors. Intradural-extramedullary lesions arise within the dural tube but are extrinsic to the spinal cord itself. Lesions in this category include meningiomas, schwannomas, neurofibromas, and leptomeningeal metastatic disease. Intramedullary lesions are those that arise primarily from the spinal cord or filum terminale. Primary cord tumors (most commonly ependymomas, astrocytomas, and hemangioblastomas) make up most of these lesions, while metastases are less common. Because of space constraints, only a few comments on spinal tumors are included here; for a more robust review of the wide variety of diseases in this category and their imaging appearances, the reader is referred to several excellent reviews from the radiology literature.[332–334]

Extradural neoplasms are common. MRI provides the best combination of lesion detection, morphologic characterization, and assessment of neural compromise. Nuclear medicine techniques such as technetium bone scan and PET scanning provide high sensitivity to lesion detection and excellent body wide assessment of tumor burden (Fig. 20.26). Nuclear medicine studies will not provide precise anatomic information regarding the compression of neural elements. CT is less sensitive than MRI in lesion detection; plain films are far less sensitive.

Extradural neoplasms may narrow the subarachnoid space (cerebrospinal fluid) as they extrinsically intrude into the central spinal canal. They exhibit diminished T1 signal, elevated T2 signal, and gadolinium enhancement on MRI. The unenhanced T1 image is the mainstay of lesion detection; normal adult marrow should be brighter than the intervertebral discs because of normal fatty marrow. Fat-saturated T2-weighted images and STIR images provide high sensitivity to lesion detection. Fat-saturated post-gadolinium images will also display extradural neoplasm with high sensitivity. On axial images, compression of the thecal sac or exiting nerve roots can be directly displayed. CT and plain films play a role in characterizing primary bone and cartilaginous tumors, including malignant lesions such as osteosarcoma, chondrosarcoma, chordoma, and benign tumors, including hemangioma, osteoid osteoma, giant cell tumor, and aneurysmal bone cyst.

Metastases are the most common extradural spine tumor, and the spinal column is the most common site of osseous metastases. An overwhelming majority of spine metastases are because of prostate, lung, and breast cancer. The thoracic spine is most commonly involved (70%), followed by the lumbar and cervical segments. Involvement of the vertebral body is the most common (85%), with less frequent spread to the paravertebral tissues or epidural space. The discs, dura, and the anterior longitudinal ligament are resistant to invasion by metastatic tumors. The posterior longitudinal ligament is more readily involved, as numerous venous channels penetrate it. Vertebral body metastases may be blastic (bone forming), lytic (destructive), or mixed. Blastic lesions are observed as ill-defined areas of increased density on plain films or CT; on MRI, blastic lesions will have low T1 and T2 signals with enhancement. Common primary tumors are prostate, carcinoid, or bladder cancer. Lytic metastases show destruction on plain films and CT, and low T1 and variable T2 signal with enhancement on MRI. Lytic metastases are most commonly produced by breast, lung, renal, and thyroid neoplasms. Mixed lytic and blastic lesions are visible in lung, breast, cervical, and ovarian primaries.

Hemangiomas are the most common spine tumor, present in 10%–12% of adults. They are frequently multiple. Typical hemangiomas are benign and of no clinical significance; they are identified by their fatty content on MRI (high T1 and T2 signal) and a corduroy appearance on plain films or CT. This is because of sparse, thickened trabeculae surrounded by fat. On axial images, this results in a polka dot appearance.

Osteoid osteomas occur in patients under the age of 30 years, and they typically present with pain, often nocturnal. Aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) can usually relieve pain. The lesion consists of a small nidus, less than 1.5 cm in diameter, surrounded by a larger zone of sclerotic reaction or soft tissue inflammation, visible on plain films or CT. The nidus is intensely enhancing on CT, MRI, or bone scan. Ten percent of osteoid osteomas occur in the spine, almost exclusively in the posterior neural arch. The lumbar spine is involved in 59% of spinal osteoid osteomas, the cervical region in 27%, and the thoracic spine in 12%. Lesions larger than 1.5 cm are considered osteoblastoma.

Myeloma is the most common malignant primary tumor of bone; it presents with bone pain in 75% of patients. It is often widespread at presentation. Its imaging appearance can range from discrete destructive lesions to diffuse loss of bone density indistinguishable from osteoporosis on plain films. CT is better able to resolve the discrete destructive lesions in trabecular or cortical bone. The MRI appearance is variable, with diminished T1 marrow signal and gadolinium enhancement in a multifocal or diffuse pattern. Compression fractures are common, and they may be indistinguishable from benign osteoporotic fractures. Single focal lesions (plasmacytomas) are expansile and lytic on imaging.

Leukemia may present with spine pain in the setting of diffuse marrow involvement and associated compression fractures. The most common imaging finding is that of diffuse marrow replacement, with osteopenia on plain films and CT, and generalized loss of the normal T1 marrow signal. Normal marrow should always be brighter than disc signal on T1 images. Focal extra-osseous soft tissue masses of leukemic tissue may be present and are termed "chloromas."

Lymphoma is a great impersonator. It can present in the spine as vertebral lesions indistinguishable from metastases, epidural soft tissue mass without bone involvement, diffuse leptomeningeal process, and primary intramedullary lesion.

Intradural-extramedullary neoplasms are situated within the dural sac, widening the subarachnoid space as they displace the cord or cauda equina; these lesions are typically benign.[94] Meningiomas typically exhibit a broad base against the dural surface and enhance uniformly. Schwannomas and neurofibromas are generally indistinguishable on imaging. They may enhance uniformly or show central zones of cystic degeneration. The classic "dumb-bell" neurofibroma may issue through and widen a neural foramen. They may also occur entirely within the dural sac or in a paravertebral location. Leptomeningeal metastatic disease is most typically seen as an enhancement on the surface of the cord or within the roots of the cauda equina. Sometimes more discrete small masses may be observed within the cauda equina. CSF cytology remains more sensitive than MRI in the detection of leptomeningeal metastatic disease.

Intramedullary neoplasms are rare entities, but they may present with pain or dysfunction that can mimic degenerative disease. Ependymomas arise from the ependymal cells lining the central

• **Figure 20.25** Spondyloarthropathy. Changes of sacroiliitis are detectable on radiographs **(A)** as irregularity, erosions, and sclerosis, dominant on the iliac side of the joint. In the end stage of ankylosing spondylitis (AS), the sacroiliac joints are fused, and sclerosis resolves **(B)**; this radiograph also depicts the dagger sign, as the fused spinous processes make a continuous sclerotic structure in the midline. Computed tomography (CT) **(C)** is more sensitive in the detection of erosions and early sclerotic reaction in AS; this structural change may simply reflect prior disease. Only magnetic resonance imaging (MRI) can detect disease activity **(D)** as demonstrated by the T2 hyperintensity in and about both sacroiliac joints in this AS patient. The gracile vertical syndesmophytes bridging lumbar vertebrae and the fused posterior elements are well seen on CT **(E)**; the spine in AS is rendered vulnerable to three-column unstable fractures with modest trauma **(F)**. These situations deserve CT imaging. The spondyloarthropathy of inflammatory bowel disease may present as back pain (T2 sagittal **[G]** and enhanced T1 fat-saturated sagittal **[H]**) with evidence of multifocal inflammatory spondyloarthropathy. The differential diagnosis here is multilevel spondylodiscitis, especially Pott's disease (tuberculosis). Changes of sacroiliitis in inflammatory bowel disease **(I)** may be indistinguishable from AS. Asymmetric sacroiliitis (T1-enhanced, fat-saturated coronal MRI **[J]**) is typical of reactive spondylarthritis (formerly Reiter's syndrome).

spinal canal of the cord. Ependymomas are the most common intramedullary tumor in adults. A specific subtype of ependymoma, the myxopapillary ependymoma, occurs in the conus medullaris and filum terminale. Because of their slow growth, they may cause osseous erosion and scalloped enlargement of the central spinal canal. MRI demonstrates an enlarged cord or filum terminale with an elevated T2 signal and heterogenous enhancement. Small cysts or hemorrhage are frequent. Astrocytomas are typically low-grade neoplasms, more commonly noted in young patients and the cervical region. They typically extend over multiple vertebral segments within the cord with poorly defined margins. The cord is enlarged with heterogenous enhancement. The entire cross-section of the cord is typically involved. Considerable edema within the white matter of the cord extends cephalad and caudal to the enhancing neoplasm itself. Peritumoral cysts may be present. Hemangioblastomas are rare lesions that typically occur in the cervical and thoracic spine. An intensely enhancing vascular nodule adjacent to the pial surface, often associated with an intramedullary cyst and relatively extensive cord edema, is typical. About one-third of patients with hemangioblastomas will have Von Hippel Lindau syndrome.

Intramedullary spinal cord metastases are less common than primary cord tumors. However, these are being increasingly diagnosed, and several enhancement features on post-gadolinium MRI have high specificity for these lesions compared to primary cord tumors: the rim, flame, and central dot signs.[335,336] Indeed, specific enhancement patterns such as these can be extremely helpful differentiating features when assessing both neoplastic and non-neoplastic causes of myelopathy.[94] Spinal cord metastases also often demonstrate considerable spinal cord edema, even if the size of the metastasis is relatively small.[337] Evidence of the primary malignancy and/or other metastatic disease may be evident, and the spinal cord metastases themselves may be multiple.[337]

Spinal Dural Arteriovenous Fistula

Spinal dural arteriovenous fistulas (AVFs) are the most common form of vascular malformation involving the spine. This lesion merits description in that it may present with pain and progressive neurologic deficit, mimicking NIC; it frequently remains misdiagnosed or undiagnosed for prolonged periods despite characteristic imaging features.[338] In Atkinson's series, the mean delay from symptom onset to diagnosis was 23 months.[339] Patients are frequently subjected to misdirected interventions, including decompressive surgery. When diagnosed, it is treatable with the arrest of the progressive neurologic deficit.

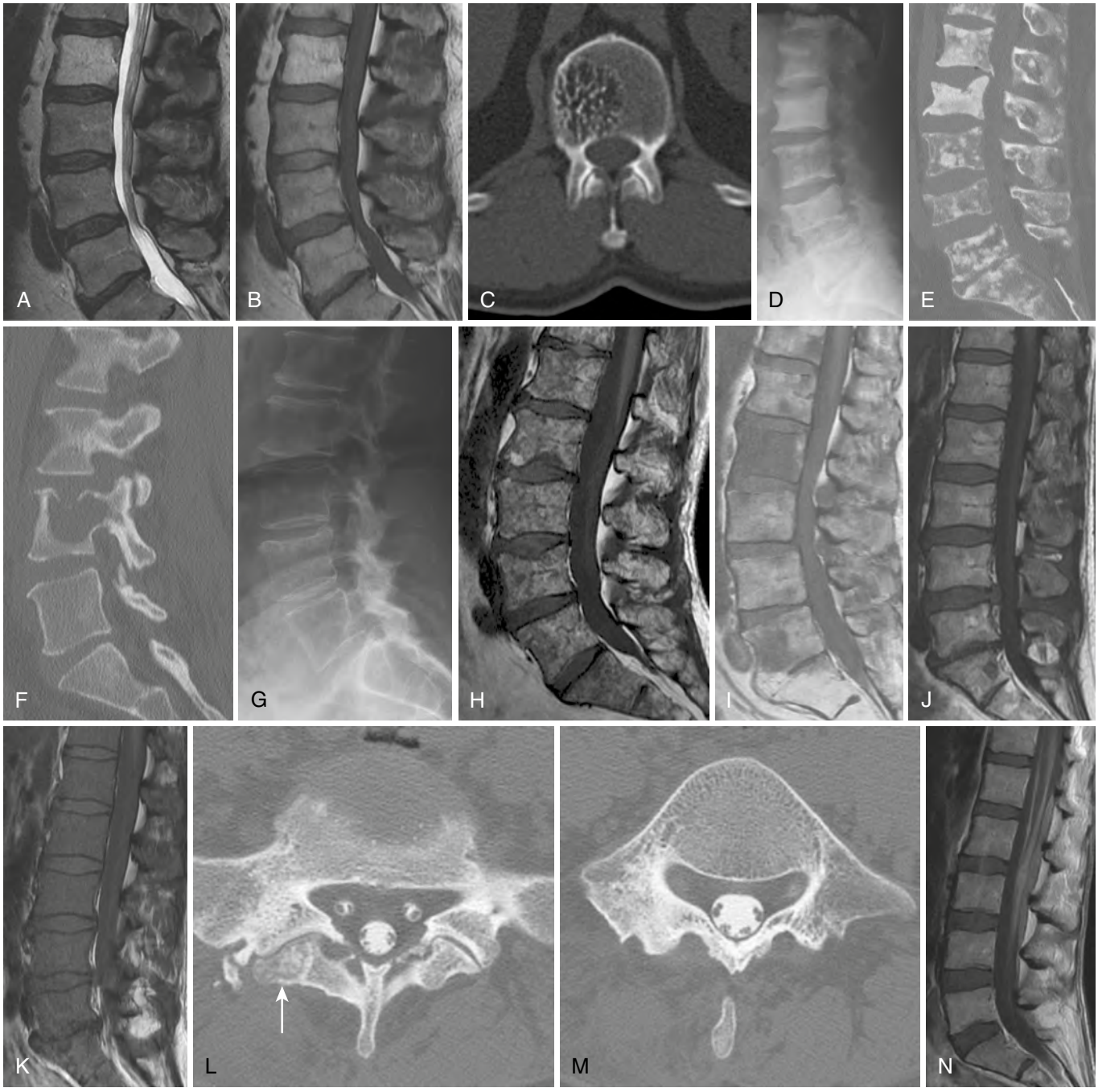
Spinal dural AVFs are an acquired lesion, with a fistulous communication within the dura of a root sleeve and intrathecal venous drainage to the venous plexus surrounding the cord. This results in venous hypertension within the cord and ultimately cord dysfunction. The fistula is most common in the low thoracic or lumbar spine. It is a lesion observed in elderly males. Gilbertson's series[340] included patients with a mean age of 62 years (range 37–81 years). Atkinson's series[339] reported a 4:1 male predominance. Pain was a reported symptom in 53% of patients. Many of these patients described a burning, dysesthetic pain in the lower extremities; 15% had low back pain when erect, which worsened with use of the lower extremities. This is typically accompanied by a slowly progressive or stepwise worsening myelopathy, manifest as lower extremity fatigue and weakness. Atkinson's series[339] reported that 69% of patients had upper and lower motor neuron signs; 30% had only lower motor neuron signs.

Imaging findings of dural AVFs have been well described.[341] On CT myelography, abnormally prominent tortuous vessels are present in 100% of cases; this may give the cauda equina a beaded appearance. There will be T2 hyperintensity in the cord on MRI in nearly 100% of cases (Fig. 20.27). This typically extends over multiple vertebral segments and may be accompanied by cord enlargement in 45% of cases. There may be patchy cord enhancement ("missing-piece" sign[342]); these findings may raise a concern for tumor. A differentiating finding is the presence of prominent T2-hypointense flow voids or intravascular enhancement caused by the dilated veins, particularly on the dorsal surface of the cord. The T2 hyperintensity in the cord usually involves the low thoracic cord and conus; this does not predict the site of the fistula, though if the conus is spared, the fistula is likely thoracic in location.[343] Magnetic resonance angiography is useful in predicting the site of the fistula (Fig. 20.27)[341] and reducing the scope of spinal angiography, which provides a definite diagnosis. For patients whose spinal dural AVF had been identified with spinal angiography, a 2014 study by Cao and colleagues demonstrated four independent predictors compared to angiography negative patients with suspected vascular diseases: age ≥50 years, length of intramedullary cord lesion ≥5 vertical segments, perimedullary dilated vessels, and sub-cervical lesion location.[344] The presence of three or more of these criteria predicted a spinal dural AVF with a sensitivity of 85% and a specificity of 97%. Once diagnosed by angiography, the fistula then may be disconnected surgically or by an endovascular approach. After treatment, progression of findings, especially worsening of parenchymal T2 hyperintensity, suggests either incomplete treatment or recurrence.[345]

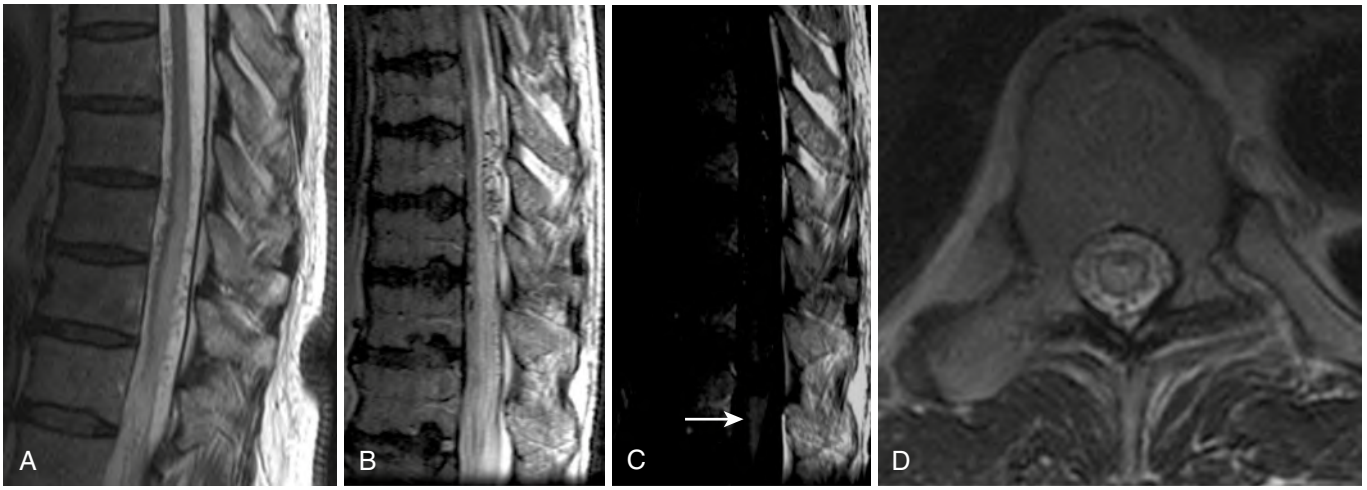
The goal of diagnosis and therapy is primarily to arrest the progression of the neurologic deficit and possibly improve the current disability. After successful occlusion of the fistula, either surgically or by endovascular embolic techniques, gait improvement was noted in 67%–80% of patients.[341] Bowel/bladder dysfunction or pain is relieved in only a minority of patients. Worsening of motor symptoms should prompt an imaging investigation for recanalization of the fistula.[341] After successful fistula occlusion, cord enlargement, enhancement, and T2 hyperintensity and the prominent veins about the conus will slowly resolve; T2 hyperintensity and enhancement may persist for up to a year. Progression of the findings should prompt a search for residual/recurrent fistula. A rare counterpart to the conventional spinal dural AVF is the spinal epidural AVF. While this uncommon condition can also present with congestive myelopathy, symptoms may rarely occur to compression from epidural venous engorgement. Based on a series of 24 patients over a ten-year period, Nasr and colleagues that the imaging findings on MRI are essentially identical to the more common spinal dural AVF, including intramedullary T2 hyperintensity and enhancement and associated intradural flow voids.[346] Meanwhile, a key differentiating factor from traditional dural AVF on angiography is the presence of a venous pouch in the epidural venous plexus.

Conclusion

As a synopsis of the imaging assessment of the patient with spine or limb pain, this chapter has ranged widely over large swaths of pathology and imaging technology. There are enduring themes. The primary role of imaging is to detect systemic disease causal of the patient's pain or neurologic dysfunction; such disease is uncommon. Currently, imaging is currently overutilized to the



• **Figure 20.26** Spine neoplasm. Sagittal T2 **(A)** and T1 **(B)** images show a lesion in the L2 vertebral body characterized by increased signal intensity on both sequences, typical of hemangioma, the most common benign spinal extradural neoplasm. A computed tomography (CT) image in another patient **(C)** demonstrates the classic CT features of hemangioma: thickened trabeculae surrounding increased marrow fat, resulting in a polka dot appearance. Blastic metastases **(D)** have increased bone density; CT is more sensitive than radiographs **(E)**, particularly in the detection of lytic metastases **(F)**. Myeloma can be challenging to detect on radiographs, mimicking osteoporosis **(G)**; magnetic resonance imaging (MRI) in the same patient **(H)** identifies the myriad of tiny destructive lesions. The MRI T1 sagittal sequence **(I)** typically reveals metastatic disease as focal hypointense lesions, as in this patient with prostate cancer, as the bright signal of normal marrow fat is replaced. When marrow replacement is diffuse, this can be difficult to detect. Normal marrow should always be brighter than adjacent discs. Note that normal marrow in **(J)** is completely replaced two years later by leukemia **(K)** when this patient presented with back pain. Osteoid osteoma is a posterior element benign neoplasm causal of pain, often nocturnal and relieved by salicylates. It is visible as a small nidus (*arrow* in **[L]**) with a surrounding sclerotic reaction **(M)**. Leptomeningeal metastases or lymphoma may be imaged as diffuse enhancing tissue coating the cord and cauda equina **(N)**.



• **Figure 20.27** Dural arteriovenous fistulae. T2 sagittal magnetic resonance images (MRIs) in two patients, **(A)** and **(B)**, both demonstrate enlargement of the conus with multisegmental T2 hyperintensity. Post-gadolinium T1 sagittal MRI (**[C]**, same patient as **[B]**) shows intravascular enhancement in the enlarged perimedullary veins and patchy parenchymal enhancement in the conus *(arrow)*. Axial T2 image through the lower thoracic cord **(D)** demonstrates increased T2 signal throughout the substance of the cord, with a dark border of diminished T2 signal at the periphery of the cord. (From Morris JM. Imaging of dural arteriovenous fistula. *Radiol Clin North Am.* 2012;50:823–839.)

detriment of patients and society. It has no value in the patient's initial presentation in the absence of red flag features suggesting systemic disease. The decision to begin imaging should be reasoned, considering the benefits of improved outcomes versus real risks and harms. The ACR and the ACP have promulgated evidence based guidelines for imaging use; they should be respected. When imaging occurs, it must be done with full appreciation of its inherent specificity and sensitivity faults. There is a high prevalence of asymptomatic, age-related change evident on all types of spine imaging; loss of T2 signal in the disc nucleus, anterior and lateral vertebral osteophytes, disc protrusions, and facet and sacroiliac joint arthrosis do not correlate with pain. Imaging performed without axial load, and physiologic posture may be insensitive to dynamic lesions. Structural alterations detected by imaging are of less significance than physiologic parameters of edema, hyperemia, disruption of blood-nerve barrier, or accelerated metabolism noted with T2 hyperintensity (STIR or fat-saturated images), gadolinium enhancement, or nuclear medicine techniques. Always treat the patient, not the images.

Acknowledgments

The authors sincerely thank Dr. Sonia Watson, Ph.D., for her assistance in reference citation management.

Key Points

- The primary role of imaging is to identify systemic disease; no imaging is indicated in the acute presentation of back or limb pain without "red flag" features.
- All spine imaging has a significant specificity fault: a high prevalence of asymptomatic age-related findings, including disc "degeneration" and facet arthrosis.
- Spine imaging performed without physiologic positioning, and axial load may be insensitive to dynamic lesions.
- Imaging correlates poorly with clinical presentation and course.
- Meticulous enumeration of spine segmentation from the skull base caudally is necessary to avoid wrong segment procedures.
- MRI findings can reasonably predict positive lumbar discography; the HIZ and significant expression of the Modic endplate change have high specificity but low sensitivity.
- Imaging cannot identify cervical discogenic pain.
- Findings of structural arthrosis of the facet or sacroiliac joints (osteophytes, joint space narrowing, sclerosis) have no relationship to pain; physiologic findings (positive bone scan, MRI T2 hyperintensity) may predict pain but have not been tested against an appropriate reference standard.
- Radicular pain requires both neural compression and an inflammatory response; standard imaging detects only the neural compression.
- There is no relationship between the size, type, or change in disc herniations over time and patient outcomes.
- The imaging natural history of disc herniation is resolution.
- NIC requires compression at multiple segmental levels or in multiple compartments (central, lateral recess, foraminal) for clinical expression.
- MRI signal changes in the cervical cord can provide prognostic guidance for decompression in the CSM patient.

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21

Biomarkers of Pain: Quantitative Sensory Testing, Conditioned Pain Modulation, Punch Skin Biopsy

JULIANE SACHAU, RALF BARON

Introduction

Identification of potential biomarkers for chronic pain is essential for correct diagnosis, prediction, and evaluation of treatment response. A biomarker is defined as a "characteristic objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] The establishment of a new biomarker should follow a standardized process and requires the definition of the exact objective, i.e. what should be measured.[2] The United States Food and Drug Administration (FDA) has defined seven types of biomarkers that can be used to assess different categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, safety (Table 21.1).[3]

The correct diagnosis is a prerequisite prior to starting a suitable pain therapy. It is, for example, important to distinguish between chronic neuropathic and chronic nociceptive pain,[4] as the treatment of these entities would be approached differently. While nociceptive pain, i.e. pain that arises from damage to non-neuronal tissue with activation of nociceptors, is likely to respond to non-steroidal anti-inflammatory drugs such as naproxen or ibuprofen, or in more severe cases opioids, treatment of neuropathic pain, i.e. pain as a direct consequence of a lesion or disease of the somatosensory system, is more challenging and requires the use of different co-analgesics, e.g. anti-convulsants, anti-depressants.

Many patients with chronic pain do not achieve adequate pain relief with available drugs. With regard to chronic neuropathic pain, the number needed to treat for a 50% pain reduction for recommended first-line agents, i.e. tricyclic anti-depressants, selective serotonin-norepinephrine reuptake inhibitors, and calcium alpha two delta agonist anti-convulsants, ranges from 3.5 to 7.7.[5] In addition, many clinical trials involving newer agents have failed to show any treatment effect. Both inadequate pain relief with already available drugs and the failure of clinical trials involving newer agents might be explained by the heterogeneous clinical picture and the numerous underlying pathophysiologic pain mechanisms. *A priori* stratification of patients using a valid predictive biomarker could help identify patients who would benefit the most from a specific drug. In addition, to modify current treatment and/or initiate further measures, it is important to forecast disease progression.

To date, no valid biomarker has been identified for use in the assessment and treatment of chronic pain. However, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recently considered three promising biomarkers for use in the development of analgesic treatments, i.e. sensory testing, skin punch biopsy, and brain imaging.[6]

In this chapter, we will focus on sensory testing, including "static" quantitative sensory testing (QST) and "dynamic" conditioned pain modulation (CPM), as well as skin punch biopsy and their role as susceptibility, diagnostic, prognostic, predictive, and pharmacodynamic biomarkers. Although sensory testing does not completely correspond to the definition of a biomarker as an objective measurement because of its psychophysical nature, it is discussed here as there are promising hints for its use as a biomarker, and at least for QST, there exists a standardized protocol with reference values.

Quantitative Sensory Testing

Sensory testing of chronic pain patients has become more relevant recently, as the heterogeneous clinical presentation of pain patients has become increasingly recognized.

Concerning neuropathic pain, patients with the same pain etiology can present with various symptoms and signs, for example, the simultaneous presence of mechanical allodynia and thermal hypesthesia in the same patient with postherpetic neuralgia. In contrast, different pain etiologies can share similar somatosensory abnormalities. The different somatosensory abnormalities are thought to reflect the underlying pathophysiologic mechanisms in chronic pain patients. For example, mechanical hyperalgesia, i.e. enhanced pain to punctate stimuli and dynamic allodynia, are thought to reflect central sensitization mechanisms, whereas increased sensitivity to heat can be related to primary hyperalgesia, i.e. peripheral sensitization of nociceptive afferents.[7]

Up to now, treatment of chronic pain has been based on the underlying etiology. However, current recognition of the heterogeneous clinical presentations of chronic pain has led to the concept of a mechanism-based therapy with stratification and treatment of patients according to the underlying pathophysiologic mechanisms.[8] An exact classification of patients according

TABLE 21.1 Categories Of Biomarkers According to the Biomarkers, EndpointS and other Tools (BEST) Glossary of the United States Food and Drug Administration (FDA)[3]

Category	Definition
Susceptibility/risk	potential for developing a disease in an individual without clinically apparent disease
Diagnostic	detect/confirm the presence of a disease or condition of interest or identify individuals with a subtype of the disease
Monitoring	assess the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent
Prognostic	identify the likelihood of a clinical event, disease recurrence, or progression in patients who have the disease of interest
Predictive	identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent
Pharmacodynamic/ response	show that a biologic response has occurred in an individual who has been exposed to a medical product or an environmental agent
Safety	measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect

to their somatosensory profile is necessary to realize this concept and might lead to improved treatment response.

Diagnostic

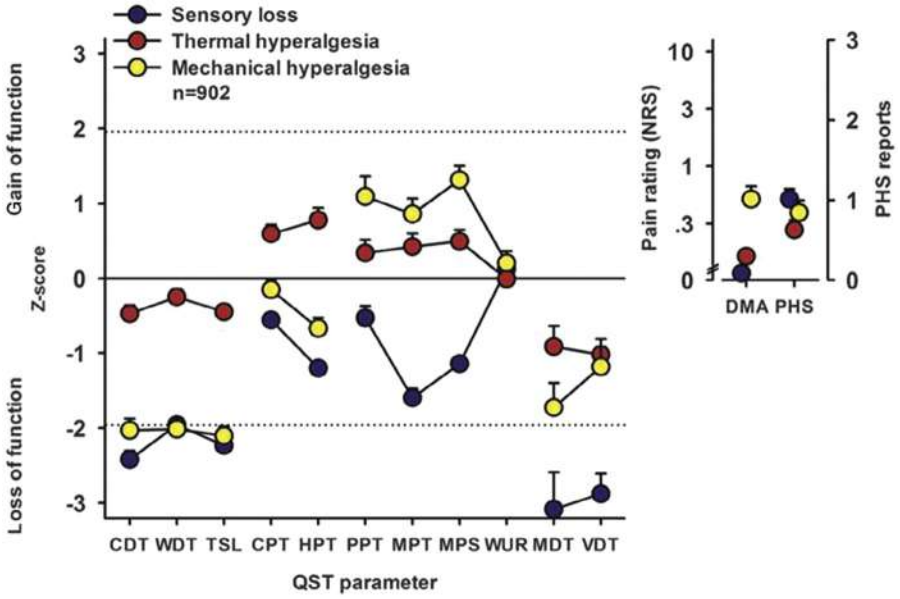
QST allows for the quantification of the somatosensory function of the peripheral and central nervous system, including non-nociceptive (Aβ-) and nociceptive fibers (Aδ- and C-fibers) by applying calibrated mechanical (e.g. graded von Frey hairs) and thermal stimuli to the skin, whose intensity or painfulness are evaluated by the patient.

Many different QST procedures, mainly thermal testing procedures, have been used in the past to assess sensory function, especially in patients with neuropathic pain. One advantage of QST is the ability to assess the entire somatosensory system, including both large and small nerve fibers, in contrast to conventional electrophysiology (electromyogram/nerve conduction studies), which primarily assess large nerve fibers. Therefore QST has been used for the early diagnosis of diabetic polyneuropathy showing abnormal vibration and thermal detection thresholds. Compared to clinical examination or nerve conduction studies, the sensitivity of QST ranges from 27%–98% for cold or 58%–84% for vibration in diabetic neuropathies.[9] Pure small fiber neuropathies are characterized by an isolated lesion of thin myelinated Aδ-fibers or unmyelinated C-fibers. Affected patients complain about burning or electric shock-like pain, tingling, pins and needles as well as impaired thermal perception. While nerve conduction studies are per definition normal in these entities, QST shows abnormal thermal thresholds indicative of small nerve fiber damage.[10] Therefore QST has been recommended as a diagnostic tool to screen for cold and warm deficits in patients with suspected neuropathy with small fiber involvement, e.g. early diagnosis of diabetic neuropathy or diagnosis of small fiber neuropathy.[9]

In addition, altered sensory function was shown to be present in different neuropathic pain etiologies such as postherpetic neuralgia (PHN) or central pain. Compared to reference data of 162 healthy controls, almost half of patients with PHN are characterized by dynamic mechanical allodynia.[11] In addition, patients frequently exhibit abnormal loss to thermal or mechanical detection parameters. QST abnormalities were also found in pain conditions other than neuropathic pain, such as fibromyalgia, chronic low back pain, osteoarthritis, and migraine. A meta-analysis of 41 studies using QST for phenotyping patients with osteoarthritis showed that decreased pressure pain thresholds at both affected and unaffected sites could differentiate between patients and healthy controls.[12] Many studies used sensory testing in fibromyalgia patients. Affected patients were shown to be characterized by altered thermal thresholds for heat and cold pain.[13,14] In addition, increased sensitivity to pressure pain is a common sign in fibromyalgia patients.[15]

The correct interpretation of sensory abnormalities in pain patients requires a standardized testing protocol and comparison to reference data of healthy controls. In 2006, the German Research Network on Neuropathic Pain (DFNS) established a standardized QST protocol to analyze the exact somatosensory phenotype of neuropathic pain patients.[16] This protocol consists of seven tests to assess 13 thermal and mechanical parameters, i.e. cold and warm detection thresholds (CDT, WDT), thermal sensory limen (TSL), paradoxical heat sensations (PHS), cold and heat pain thresholds (CPT, HPT), mechanical detection threshold (MDT; von Frey filament 0.25-512 mN), mechanical pain threshold (MPT, pinprick stimulators, 8-512 mN), mechanical pain sensitivity and dynamic mechanical allodynia (MPS and DMA; pinprick stimulators, standardized brush, cotton wisp, cotton wool tip), wind-up ratio (WUR), vibration detection threshold (VDT; Rydel-Seiffer graded tuning fork, 64 Hz, 8/8 scale), pressure pain sensitivity (PPT; pressure gauge device) (Fig. 21.1).

A database with reference values for different body regions (face, dorsum of the foot, dorsum of the hand, trunk) was implemented[11,17] that allows direct comparison of patients with age- and sex-matched healthy controls. For this purpose, Z-transformation of every single parameter was performed (except for DMA, PHS), resulting in a QST profile where all parameters are presented as standard normal distribution independent of the different units. Z-values of zero represent a value corresponding to the mean of healthy controls. Z-values below zero indicate a loss of function, i.e. lower sensitivity compared to controls (hypoalgesia, hypoesthesia). Z-values above zero indicate a gain of function, i.e. higher sensitivity (hyperalgesia, hyperesthesia). A z-score of 0±1.96 represents the range that can be expected to include 95% of healthy control subject data (95% confidence interval). Z-values outside this 95% confidence interval are considered as absolute



• **Figure 21.1** Subgroup analysis of neuropathic pain. (Adapted from Baron et al.[19]). Sensory profiles of the three clusters presented as mean z-scores ± 95% confidence interval for the test data set (n = 902). Note that z-transformation eliminates differences because of test site, sex, and age. Positive z-scores indicate positive sensory signs (hyperalgesia), whereas negative z-values indicate negative sensory signs (hypoesthesia and hypoalgesia). *Dashed lines*: 95% confidence interval for healthy subjects (–1.96 < z < +1.96). Note that if the mean of a cluster is within the *shaded area*, this does not imply that it does not differ from a healthy cohort. Values are significantly different from those of healthy subjects if their 95% marked interval does not cross the zero line. *Insets* show numeric pain ratings for dynamic mechanical allodynia (DMA) on a logarithmic scale (0-100) and frequency of paradoxical heat sensation (PHS) (0-3). *Blue symbols:* cluster one "sensory loss" (42%). *Red symbols:* cluster two "thermal hyperalgesia" (33%). *Yellow symbols:* cluster three "mechanical hyperalgesia" (24%). *CDT*, cold detection threshold; *CPT*, cold pain threshold; *HPT*, heat pain threshold; *MDT*, mechanical detection threshold; *MPS*, mechanical pain sensitivity; *MPT*, mechanical pain threshold; *NRS*, Numerical Rating Scale; *PPT*, pressure pain threshold; *QST*, quantitative sensory testing; *TSL*, thermal sensory limen; *VDT*, vibration detection threshold; *WDT*, warm detection threshold; *WUR*, wind-up ratio.

abnormalities (<–1.96 abnormal loss, >1.96 abnormal gain).[18] Investigation of a large cohort of patients with different neuropathic pain symptoms revealed the presence of different combinations of loss and gain across all investigated pain etiologies.[18] QST cluster analysis in patients with peripheral neuropathic pain of different etiology revealed the presence of three subgroups of patients that were characterized by different sensory profiles (Fig. 21.1).[19] The first cluster, "sensory loss," was characterized by a loss of small and large fiber function in combination with PHS; the second cluster, "thermal hyperalgesia," showed preserved sensory functions in combination with heat and cold hyperalgesia and mild dynamic mechanical allodynia; and the third cluster, "mechanical hyperalgesia," was characterized by a loss of small fiber function in combination with pinprick hyperalgesia and dynamic mechanical allodynia. The three clusters were distributed across all included neuropathic pain etiologies. However, with different frequencies, e.g. the sensory loss cluster was the most frequent cluster in patients with polyneuropathy (about 51.8%), whereas patients with PHN were especially characterized by mechanical hyperalgesia, i.e. cluster three (46.6%). Interestingly, similar clusters were identified in human surrogate pain models,[20] which supports the concept of a mechanism-based stratification approach.

According to the updated grading system for neuropathic pain proposed by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG), a confirmation of sensory signs is necessary to raise the certainty of neuropathic pain presence from "possible" to "probable," which can be sometimes only obtained using QST.[21] However, only a few studies have examined the sensory profile in painful versus painless neuropathy so far.[22] As their results showed similar thermonociceptive impairment in both cases, QST seems limited in its ability to differentiate between neuropathy without pain and neuropathic pain.

Prognostic

There is evidence that QST has a prognostic value. For example, thermal deficits as indicative of small nerve fiber loss were associated with painfulness of diabetic neuropathy,[23] while mechanical deficits were shown to predict the development of foot ulcerations.[24] The prognostic value of QST was also demonstrated in a group of patients with colorectal cancer who were examined by QST before receiving oxaliplatin-based chemotherapy and were then followed up for 26 weeks.[25] Pretreatment touch sensation deficits were found to predict severity and painfulness of oxaliplatin-induced neuropathy.

Susceptibility/Predictive

In addition, QST seems to be a promising susceptibility and predictive biomarker for chronic pain (for definition, see Table 21.2). A recent prospective study aimed to identify potential risk factors

TABLE 21.2 Quantitative Sensory Testing Parameters and Suspected Location of the Underlying Pathophysiologic Mechanisms

QST Parameter	QST Testing Device	Suspected Location of an Underlying Pathophysiologic Mechanism: Peripheral	Suspected Location of an Underlying Pathophysiologic Mechanism: Central	QST Finding
Thermal				
Detection threshold for innocuous thermal stimuli (cold, warm)	Thermotest	Aδ (cold) C (warm)	Spinothalamic	Increased thermal detection threshold, i.e. cold/warm hypoesthesia Decreased thermal detection threshold, i.e. cold/warm hyperesthesia
Detection of the threshold for noxious thermal stimuli (cold, heat)	Thermotest	(Aδ) C	Spinothalamic	Increased thermal pain threshold, i.e. cold/heat hypoalgesia/analgesia Decreased thermal pain threshold, i.e. cold/heat hyperalgesia
Paradoxical heat sensations	Thermotest		Central disinhibition	Heat sensation as a response to a cold stimulus
Mechanical				
Detection threshold for innocuous mechanical stimuli (static light touch)	Calibrated von Frey hairs	Aβ	Lemniscal	Increased mechanical detection threshold, i.e. mechanical hypoesthesia Decreased mechanical detection threshold, i.e. mechanical hyperesthesia
Detection threshold for innocuous vibration	Graduated tuning fork	Aβ	Lemniscal	Increased vibration detection threshold
Detection threshold for noxious mechanical stimuli (pinprick)	Calibrated needles, e.g. pinprick stimulators	Aδ	Spinothalamic	Increased mechanical pain threshold, i.e. pinprick hypoalgesia/analgesia Decreased mechanical pain threshold, i.e. pinprick hyperalgesia
Pain rating suprathreshold stimulation	Calibrated needles, e.g. pinprick stimulators	Aδ	Spinothalamic	Decreased pain/absent pain, i.e. pinprick hypoalgesia/analgesia Increased pain, i.e. hyperalgesia
Dynamic mechanical allodynia	Cotton wool, Q-tip, brush	Aβ	Lemniscal	Allodynia, i.e. pain because of a normally non-painful stimulus
Pain induced by repetitive stimulation (wind-up ratio)	Calibrated needles, e.g. pinprick stimulator		Spinothalamic	Temporal summation
Blunt pressure	Algometer	Aδ, C	Spinothalamic	Increased pressure pain threshold, i.e. pressure hypoalgesia Decreased pressure pain threshold, i.e. pressure hyperalgesia

for PHN via characterization of the sensory profile and physical and psychosocial functioning during acute herpes zoster.[26] The sensory profile at the affected site and a distal contralateral control site (four dermatomes above or rostral) of 74 patients with acute herpes zoster was compared to 20 healthy controls. Patients with PHN at the six-month follow-up point, defined as persisting pain in the affected area (22.4%), were then compared to those without PHN. Besides older age, higher pain intensity, reduced quality of life, and physical functioning during acute herpes zoster, the development of PHN seems to be predicted by sensory alterations. The authors concluded that mechanical hyposthesia and/or hyperalgesia/mechanical allodynia combined with preserved thermal detection, especially at body sites distal to the acute herpes zoster area, may be potential risk factors for PHN.

A priori stratification of patients according to their sensory profile could help to predict treatment response in clinical trials and clinical practice. Consequently, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has acknowledged the sensory subgrouping of patients by use of standardized QST, an adequate stratification tool for determination of specific sensory phenotypes of patients in clinical trials on neuropathic pain.[27] Although no analgesic drug has been developed based on the prediction by sensory testing, several studies have reported promising results. In a Phase 2a proof of concept study with retrospective phenotyping of patients with painful diabetic neuropathy, a novel selective TRPA1 antagonist (GRC 17536) was shown to be effective, especially in patients with preserved sensory function (irritable nociceptor).[28] A retrospective analysis of a randomized

controlled trial investigating the effect of pregabalin vs. placebo in patients with painful human immunodeficiency virus (HIV) neuropathy showed significant pain reduction only in a subgroup of patients with marked pinprick hyperalgesia (corresponding to QST cluster three). In contrast, there was no difference in the entire patient cohort.[29] In a first placebo-controlled trial with *a priori* phenotype-stratification, oxcarbazepine was more effective for relief of neuropathic pain in patients with the "irritable nociceptor" phenotype defined as hypersensitivity and preserved small nerve fiber function (corresponding to QST cluster two) compared to the "non-irritable phenotype" (NNT for 50% pain relief: 3.9 vs. 13).[30] However, the same authors failed to show a phenotype-dependent treatment effect of 5% lidocaine patch in patients with peripheral neuropathic pain because of PHN or peripheral nerve injury using the same patient stratification (irritable vs. non-irritable phenotype).[31] An additional prospective crossover study investigated the effect of pregabalin versus placebo in patients with painful chemotherapy induced neuropathy.[32] At baseline, all study participants received sensory testing on the dorsum of the feet, assuming that patients with increased mechanical pain sensitivity would more likely respond to treatment with pregabalin. Since there was no correlation of the MPT with the analgesic response, the authors concluded that the MPT was not a useful treatment predictor in this specific case.

To examine the value of predictive sensory testing, future trials of drug development will need to include a prospective stratification of patients according to their somatosensory profile.

Besides the above-mentioned advantages, several limitations should be kept in mind when performing and interpreting QST (Table 21.3). One major limitation is that QST only assesses stimulus-evoked negative and positive sensory phenomena, whereas spontaneous pain is not detectable. Since the whole somatosensory pathways are assessed, QST cannot determine the exact localization of the lesion, i.e. peripheral versus central. Finally, as a psychophysical method, QST depends on the patient's cooperation and may be influenced by psychological factors that may result in false-negative findings. Therefore it is even more important to use a standardized testing protocol with standardized stimuli and instructions and reference values of healthy controls. Because of high commitments of time and costs and the need for a good training to ensure standardization, the DFNS QST protocol is only used by certain centers. To overcome these limitations, easy-to-use bedside protocols have recently been presented that enables increased applicability of sensory testing in clinical practice and clinical trials of drug development.[33,34]

TABLE 21.3 Advantages and Limitation of QST

Advantages	Limitations
Non-invasive	Psychophysical method
Examination of large and small fibers	No information about the localization of the lesion (central versus peripheral)
Assessment of gain and loss of function	No information about the extent of the lesion (predefined testing area)
Characterization of sensory phenotypes	Only stimulus-evoked phenomena, not spontaneous pain
Standardized German Research Network on Neuropathic Pain (DFNS) protocol with reference values	Standardized DFNS protocol needs training, is time-consuming, and cost intensive
Subgrouping of patients	

Conditioned Pain Modulation

Endogenous descending inhibitory and facilitatory pathways originating in the brain can modulate the function of nociceptive neurons in the dorsal horn of the spinal cord. One important descending inhibitory pathway that suppresses the firing of convergent second-order neurons, i.e. wide-dynamic range neurons in the dorsal horn of the spinal cord, by a noxious stimulus has been first described by Le Bars et al. as diffuse noxious inhibitory controls (DNIC) in rats.[35] An expert opinion consensus has recommended the term "CPM" as the human counterpart of DNIC to describe the psychophysical paradigm in which a conditioning stimulus is used to affect a test stimulus."[36] In contrast to QST, which focuses mainly on static parameters (except for temporal summation), CPM is a dynamic measurement.

In general, CPM paradigms consist of the evaluation of a painful test stimulus first alone and afterwards during (parallel paradigm) or immediately after a painful conditioning stimulus (sequential paradigm). An intact CPM effect describes a reduction in pain intensity of the test stimulus induced by the conditioning stimulus (pain inhibits pain phenomenon).

Numerous different CPM protocols exist using different test and conditioning stimuli. Hot or cold water immersion is the most commonly used conditioning stimulus, whereas a variety of thermal, mechanical, and electrical stimuli is used as test stimulus.[37] A schematic of a possible CPM protocol is shown in Fig. 21.2.

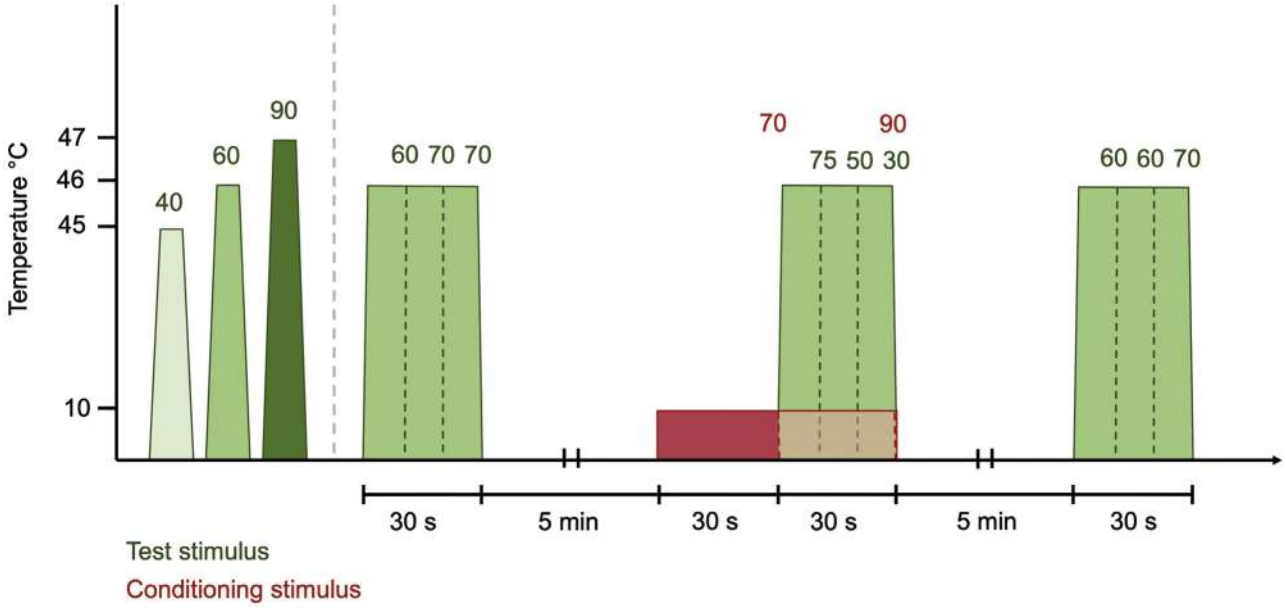
Diagnostic

Many different chronic pain syndromes are characterized by less sufficient CPM, e.g. fibromyalgia syndrome, irritable bowel syndrome, migraine, and osteoarthritis.[38] In a study investigating 96 fibromyalgia patients and 71 healthy controls, heat stimulation was used as the test stimulus and the cold pressor test as the conditioning stimulus.[39] Patients showed reduced CPM compared to controls with a good specificity (78.9%) but low sensitivity (45.7%), suggesting impaired CPM in a subgroup of fibromyalgia patients. Patients with irritable bowel syndrome were also shown to exhibit less sufficient CPM than healthy controls in several studies. For example, a study that used phasic heat as a test stimulus on the one hand and painful cold water as a conditioning stimulus on the other one showed smaller CPM in 27 premenopausal females compared to 21 age-matched controls.[40] Another study used rectal distension as a test stimulus and cold water (foot) as a conditioning stimulus.[41] However, abnormal CPM effects must be interpreted with caution as no normative values have been published so far, and a high inter-individual variability is even present in healthy subjects (see below).

Susceptibility/Predictive

CPM may also serve as a potential susceptibility biomarker for the development of chronic pain. A less efficient CPM was shown to be associated with a higher risk of chronic postoperative pain after thoracotomy[42] and abdominal surgery.[43]

Like QST, CPM may predict the treatment response of chronic pain patients via the identification of subgroups with altered endogenous pain modulation. The pharmacologic basis of CPM is not



• **Figure 21.2** Schematic of a conditioned pain modulation protocol with heat as the test stimulus and cold water immersion as the conditioning stimulus. Examples of pain intensity ratings (0–100 NRS, 0 = no pain, 100 = worst imaginable pain) are shown above the stimuli. The temperature of the heat stimulus is selected by applying three heat stimuli of 45°C, 46°C, and 47°C to the dominant volar forearm. The subject is asked to rate the pain intensity of each stimulus on a 0–100 NRS. The temperature with an intensity of 60 ± 5 is used as the test stimulus (here: 46°C). The test stimulus is applied for 30 s with pain ratings every 10 s. After 5 min, a 60 s conditioning stimulus (spread-fingered non-dominant hand in 10°C cold water immersion) is delivered and rated after 30 and 60 s. During the last 30 s the test stimulus is applied and rated again every 10 s. The application of the test stimulus is repeated after 5 min.

yet completely understood. However, investigation of DNIC in animals suggests the involvement of noradrenergic and serotonergic pathways.[44] In a study by Yarnitsky et al. baseline CPM was shown to be correlated with the efficacy of duloxetine, a serotonin-noradrenalin reuptake inhibitor, in patients with painful diabetic neuropathy.[45] Less efficient CPM at baseline predicted better duloxetine efficacy, i.e. self-reported effect of the drug on pain and greater pain reduction. Another study investigated the predictive effect of CPM and QST (dynamic mechanical allodynia, pressure, and thermal pain thresholds, temporal summation) on response to spinal cord stimulation.[46] A reduced CPM, as well as less enhanced central sensitization (pain hypersensitivity), predicted less self-reported pain three months after implantation. In patients with knee osteoarthritis, the combination of preoperative impaired CPM and facilitated temporal pain summation was associated with less postoperative pain relief 12 months after total knee replacement.[47]

Pharmacodynamic

Different studies indicate a role of CPM as a potential pharmacodynamic biomarker, i.e. to measure and monitor treatment effect. In a study by Yarnitsky et al. CPM was shown to be modified in response to duloxetine treatment, i.e. a greater improvement of CPM (baseline compared to posttreatment) was associated with greater drug efficacy. However, these results were not compared to placebo. The potential pharmacodynamic role of CPM was also shown in a placebo-controlled study of tapentadol, a μ-Opioid receptor agonist and noradrenaline reuptake inhibitor, in painful diabetic neuropathy.[48] At baseline, patients did not show significant CPM response. However, after four weeks of treatment, the tapentadol group developed significant CPM together with greater pain relief than the placebo group.

The CPM effect is affected by several factors.[49] It is dependent on age and sex, i.e. a stronger CPM effect was observed in younger adults (reduction starting in middle-age from about 40 years[50]) and in men. In women, it is influenced by the menstrual cycle phase. Attention and positive expectation are positively correlated with the CPM effect. Finally, the CPM magnitude is influenced by the paradigm itself. Higher evoked pain intensities and longer duration of the conditioning stimulus cause a stronger CPM. The modality of the conditioning stimulus is also relevant, e.g. a cold pressor test was shown to induce a stronger CPM effect than cuff-pressure and heat pain stimulation.[51]

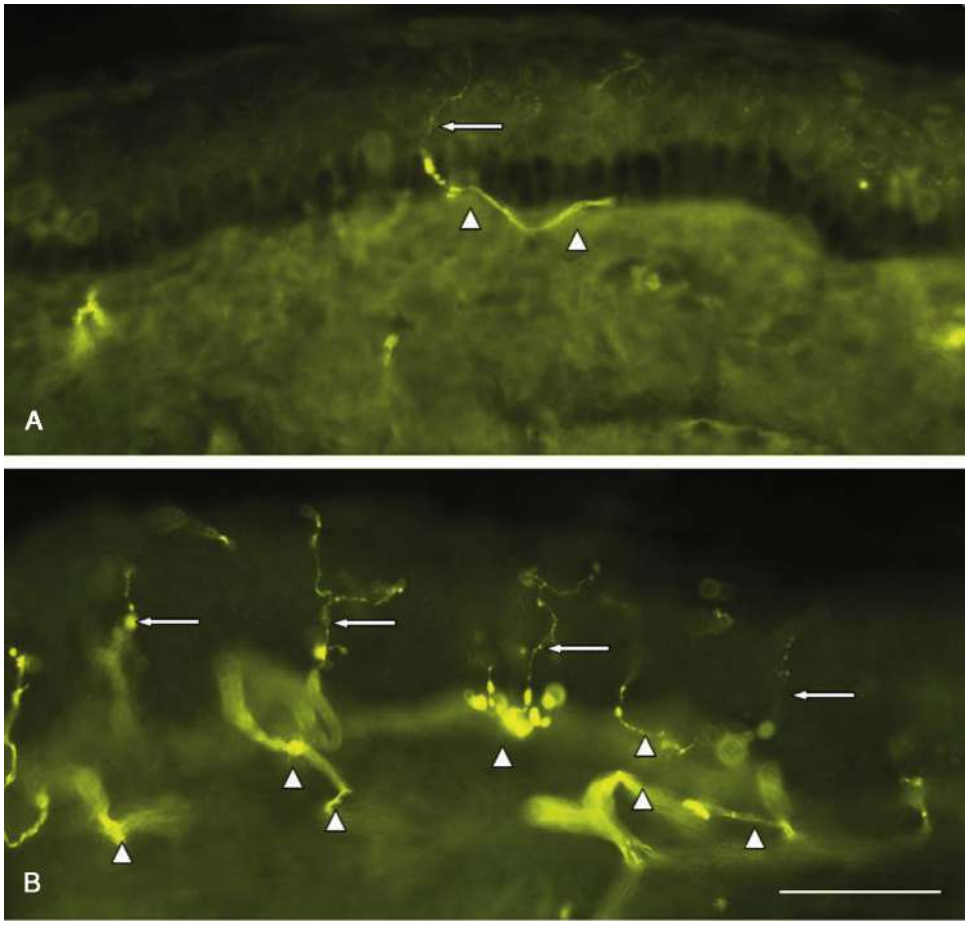
These factors can complicate the interpretation of CPM in chronic pain states. While some of them are difficult to influence, e.g. patients' expectations, standardization of the testing protocol would enable the conduction of meta-analyses with a comparison of data from different studies and thus could improve reliability. Because of the current lack of a "gold standard" CPM protocol, an expert forum has proposed recommendations regarding the practice of CPM,[52] i.e. use of an additional test stimulus or an additional standard CPM protocol. It has also been discussed that a sequential protocol is superior to a parallel one as it provides a cleaner representation of pain modulation, although this consideration has been questioned in a review by Kennedy et al. who declared that there is insufficient evidence for a greater reliability of one paradigm over another at present.[53] However, standardization of the CPM protocol is a prerequisite for its use as a biomarker and the subject of current research.

Skin Punch Biopsy

In contrast to sensory testing, skin punch biopsies are an objective measurement that can be used to investigate the nervous system and may serve as a potential biomarker, especially because they are less invasive than nerve biopsies, safe, and almost painless. Skin punch biopsies can be obtained from the hairy skin to assess the unmyelinated and thinly myelinated nerve fibers, as well as from the glabrous skin to assess large myelinated fibers. While a punch of 3–4 mm is sufficient to examine the epidermal nerve fibers, deeper biopsies of approximately 5–6 mm are required to examine sweat glands or hair follicles. To quantify the intraepidermal nerve fiber density (IENFD), sections of the biopsy are immunohistochemically labeled with the protein gene product (PGP) 9.5 antibody, a pan-axonal marker directed against ubiquitin carboxy-terminal hydrolase and highly specific in neurons.

Diagnostic

In neuropathies affecting small caliber nerve fibers, skin punch biopsies with the determination of the IEFND can serve as a diagnostic biomarker to identify neuronal loss. In small fiber neuropathies, neuronal denervation occurs in a length-dependent manner, which can be detected by a skin biopsy (Fig. 21.3). IENFD normative values exist for different biopsy techniques and different body sites. In a large multicenter study of 550 healthy participants, age and sex-dependent normative IENFD reference values at the distal leg were established for use in clinical practice and research.[54] It was shown that the IENFD declines with age and may be lower in men than in women. McArthur et al. performed skin biopsies in 98 healthy controls and 20 patients with neuropathy.[55] An IENFD below the 5th percentile of healthy controls was defined as abnormal. At the distal leg, this cutoff value results in an overall diagnostic accuracy, i.e. patients that were correctly classified via IENFD, of 88%, with a positive predictive value of 75%, a negative predictive value of 90%, a sensitivity of 45%, and a specificity of 97%. The relatively low sensitivity indicates that a normal IENFD does not exclude the presence of sensory neuropathy. For example, IENFD was within the normal range in about 10% of patients diagnosed with small fiber neuropathy based on clinical findings plus abnormal thermal thresholds at the foot.[56] In general, data on sensitivity and specificity of skin punch biopsies vary in different studies depending on the definition of small fiber neuropathy. Furthermore, altered IENFD was detected in conditions other than small fiber neuropathies, i.e. widespread pain conditions like fibromyalgia.[14] A recent study by Devigili et al. re-investigated the criteria for the diagnosis of small fiber neuropathy.[57] The authors concluded that the combination of clinical examination, QST, and IENFD is a reliable diagnostic tool in clinical practice and research. They further showed a higher diagnostic



• **Figure 21.3** Sections from 50 µm skin punch biopsies of the lower leg immunoreacted for PGP 9.5 with Cy3 as a chromophore. *Arrows* indicate examples of intraepidermal nerve fibers. *Arrowheads* show parts of the subepidermal nerve plexus. **A,** from a patient with small fiber neuropathy, only one intraepidermal nerve fiber visible. **B,** from a healthy control person. Bar = 50 µm. (Figure provided by Prof. Dr. Claudia Sommer.)

accuracy of IENFD compared to QST, depicted by a higher area under the receiver operating characteristic curve (0.90 vs. 0.58). In 2010, the European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS) declared that skin biopsy with IENFD quantification is a reliable technique to confirm the diagnosis of small fiber neuropathy.[58] It has been recommended to perform a skin punch biopsy at the distal leg, i.e. 10 cm above the malleolus lateralis, which may be accompanied by an additional biopsy from the proximal thigh (20 cm below the anterior iliac spine) to evaluate the length dependency of the neuropathy.

Besides diagnosis of pure small fiber neuropathies, skin biopsies may be used as a potential biomarker for the early diagnosis of neuropathies, where damage of small fibers may precede large fiber loss.[6] Furthermore, in PHN, cutaneous innervation is usually reduced in the affected skin compared to the mirror-image area.[59] However, a significant proportion of PHN patients have similar fiber densities in both the affected and the mirror-image skin, suggesting that the symptoms of pain and sensory dysfunction are not because of a mere loss in overall innervation density.[60] Using simple counts of anti-PGP labeled fibers, Oaklander and colleagues demonstrated that the average cutaneous fiber density was lower in subjects with established PHN than in those who had recovered without PHN after herpes zoster. Furthermore, mirror-image skin had lower fiber densities than distant control skin in subjects with established PHN.[60] Using a combination of results from a skin biopsy and testing of sensory function has helped characterize phenotypical subtypes in PHN.

It should be noted that the IENFD has been used in particular to diagnose peripheral neuropathies, whereas the possibility to distinguish between painful and painless neuropathies remains controversial. While patients with painful diabetic neuropathy were shown to have lower IENFD than those without pain in one study,[61] an observational study comparing 191 patients with painful and painless diabetic neuropathies showed a reduced IENFD in all patients without distinction between the two groups.[62] In this study, reduction of IENFD did not correlate with pain intensity. Future studies are necessary to elucidate the relationship between IENFD and pain, focusing on other protein and RNA analysis parameters. For example, different microRNA patterns were shown for painful versus painless neuropathies.[63]

Prognostic

There is some evidence that disease progression can be evaluated with skin biopsies. A prospective longitudinal study of HIV-infected patients showed that a lower nerve fiber density in the distal leg was associated with the development of a symptomatic neuropathy six to 12 months after baseline examination.[64] Beside the count of epidermal nerve fibers, skin biopsies allow the quantification of nerve fiber morphology, i.e. axon swelling, which seems to be a pre-degenerative change preceding IEFND reduction.[65] More pronounced swellings were shown to be associated with a decline in nerve fiber density and a higher probability to develop neuropathic symptoms over time in patients with neuropathy.[66]

Predictive

Only a few studies have investigated the role of skin biopsies as a potential biomarker to predict treatment response in pain. Herrmann and colleagues performed a retrospective study of patients with a painful distal sensory polyneuropathy who have been treated with a 5% lidocaine patch.[67] There was no association of the degree of epidermal or subepidermal fiber denervation at the distal leg with self-reported treatment response, implying that skin biopsy cannot predict response to the lidocaine patch. In addition, some patients exhibited a pain reduction in response to the lidocaine patch, although they were shown to have a complete nerve fiber loss. The authors concluded that the epidermal nerve innervation is not an essential substrate for the therapeutic response to lidocaine. In contrast, a retrospective study by Saperstein et al. demonstrated that patients with confirmed small fiber neuropathy (i.e. abnormal skin biopsy) were more likely to exhibit pain and to respond to standard neuropathic pain medications compared to patients with normal skin biopsies.[68] The regeneration potential of nerve fibers (spontaneous or treatment-induced) further indicates that skin biopsy can be used as an outcome parameter in clinical trials to investigate the effect of neuroprotective agents. Application of capsaicin, an ingredient of hot chili pepper and agonist of the vanilloid one receptor (TRPV1), to the skin induces short-term nerve fiber degeneration followed by spontaneous regeneration of epidermal nerve fibers with the restoration of evoked pain sensation after approximately three weeks.[69] Nerve fiber regeneration was also shown in patients with prediabetic neuropathy after one year following lifestyle interventions.[70]

Pharmacologic treatment of neuropathic pain with first-line drugs (anti-depressants, gabapentin, pregabalin) is often limited because of the systemic side effects such as dizziness or sedation.[5] Therefore topical agents have become an alternative treatment option, especially in elderly patients with localized peripheral neuropathic pain and a higher risk of fall. The application of capsaicin 8% patches can reduce neuropathic pain that lasts up to 12 weeks. To realize the concept of individualized pain therapy, current research focuses on identifying biomarkers to predict treatment response to high dose capsaicin patches. Anand et al. assessed the effect of capsaicin 8% patch in 16 patients with painful chemotherapy induced neuropathy comparing baseline and three months follow-up data of conventional neurophysiology, QST parameters, and different skin biopsy markers, among others, against PGP 9.5, TRPV1, and GAP-43 for regenerative nerve fibers.[71] Posttreatment skin biopsies showed a normalization of PGP 9.5 fibers and TRPV1 and GAP-43 fibers indicating that capsaicin application can induce nerve fiber regeneration. These results support the role of skin biopsies as a prognostic biomarker and can also be used to investigate further the predictive value of different skin biopsy markers for treatment with capsaicin.

Overall, however, there is currently insufficient data about the evidence of skin biopsy as a predictor of treatment response.

Similar to sensory testing, there are several caveats of skin biopsy techniques that should be considered. Skin biopsies predominantly provide information about the pathology in the skin, whereas changes in the afferent innervation of deep somatic structures and central changes cannot be assessed. It further remains to be determined whether the pathology in a single biopsy is representative of the entire affected area.

Summary

To date, no valid biomarkers have been identified for pain. However, there are some hints for potential candidates: sensory testing including QST and CPM as well as skin punch biopsy. Each of these methods provides both advantages as well as limitations. QST allows for the subgrouping of patients according to their pathophysiologic mechanism and may thus be helpful in realizing the concept of a mechanism-based therapy, although its validity may be limited because of its psychophysiologic character. In

contrast, a skin punch biopsy is an objective measurement. Nevertheless, its role as a diagnostic biomarker is limited since there is insufficient information about the differentiation of painful and painless neuropathies. In this chapter, we concentrated only on selected measures. However, other tools, such as electrophysiology, brain imaging, or omic assays (for example, genomic, epigenomic, metabolomic), may serve as potential pain biomarkers as well. Composite biomarkers, i.e. the combination of different methods that incorporate biologic and behavioral testing procedures, is a promising approach that may further help improving pain diagnosis and therapy.

The establishment of biomarkers in the pain field is essential for the correct diagnosis, monitoring, and treatment of pain and should therefore be increasingly the focus of scientific research.

Key Points

- Standardized and validated biomarkers are needed to improve the diagnosis of pain, predict treatment response, and monitor disease progression; promising tools are sensory testing, i.e. QST and CPM, and skin biopsy.
- A prerequisite for the establishment of a biomarker is the definition of its objective and the pain condition that should be addressed.
- The psychophysiologic character of sensory testing should be considered when using it as a biomarker for pain.
- A standardized QST protocol with reference values exists that enables direct comparison of pain patients with healthy controls
- QST allows the stratification of pain patients according to their sensory profile reflecting the underlying pathophysiologic pain mechanism.
- CPM is a dynamic measurement of the endogenous pain-inhibitory control system.
- A standardized protocol is needed to explore further the potential role of CPM as a pain biomarker.
- Skin biopsies, including quantification of intraepidermal nerve fiber density and morphologic changes, are an objective measurement for the evaluation of the peripheral nervous system.
- Further studies on skin biopsies are needed to clarify the possibility to distinguish between painful and painless neuropathies.
- Future studies should focus on composite biomarkers, i.e. combination of different measurements.

Suggested Readings

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22

Psychological and Behavioral Assessment

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Psychological and Behavioral Assessment

Chronic pain presents two broad challenges to proper assessment: 1) pain is personal and subjective, and 2) chronic pain impacts a wide range of patient functioning. These challenges necessitate a systematic approach to the standardized assessment of multiple domains of functioning using several assessment techniques, including interviews, questionnaires, behavioral observation, psychophysiologic measurement, diary data, and reports of significant others. This chapter will begin with a brief discussion of the clinical goals of psychological and behavioral assessment of patients with persistent pain, provide a rationale and context for the use of psychological assessment in the practice of pain management, articulate recommendations for the core domains of assessment, and provide an overview of the psychological assessment process. The chapter will then provide specific information about some of the most commonly employed psychological and behavioral assessment strategies for general use across chronic pain conditions. Finally, the chapter will provide information about the assessment of chronic pain in specific populations (e.g. pediatrics, older adults, and patients with mild cognitive impairment). Disease-specific measures may also be of interest to the clinician but are not specifically covered in this chapter. Examples include the Oswestry disability questionnaire (lower back pain),[1] Western Ontario and McMaster Universities osteoarthritis index (osteoarthritis),[2] and the neuropathic pain scale (neuropathic pain).[3]

Clinical Objectives

A multidimensional psychological and behavioral assessment of patients with pain can assist a multi-disciplinary pain team or treating clinician in several ways. Multidimensional assessment serves as a foundation for treatment planning and subsequent evaluation of treatment outcomes. An important outcome of the assessment process is the development of specific, measurable, achievable, relevant, and time-based patient-centered goals for treatment.[4] Data gathered in the assessment process provide important information about patients' pain experiences, pain treatment history, current, and past emotional and physical functioning, and beliefs about pain. Assessment allows the clinician to identify patients' strengths and weaknesses and the factors that contribute to the development and maintenance of problems in physical, social, and emotional functioning. Psychological and behavioral assessment may also reveal the need for adjunctive psychological treatment of preexisting or emerging psychosocial difficulties that may interfere with treatment. Psychological assessment can provide information about patients' motivation and readiness to engage in treatment and the patients' treatment preferences. Psychological assessment can also provide data about a patients' suitability for surgical or other invasive procedures under consideration.

A thorough assessment of a patient's pain complaint and functioning at baseline provides an important benchmark against which the efficacy of future treatments can be measured. Assessment should not stop after the initial visit but should be ongoing throughout the treatment process. This allows for the identification of new problems, quantifies progress across domains, and facilitates the refinement or revision of treatment if necessary. Posttreatment assessment is imperative to evaluate the overall success of the treatment and the differential success of the treatment across various domains of functions such as pain intensity, social, emotional, and physical functioning.

When making a request for a psychological and behavioral assessment, it is necessary to explicitly state the reasons for the request or pose a question about the patient or his/her treatment. It is helpful for the psychologist or behavioral specialist to understand the specific question the clinician or team is trying to answer about a patient to do a thorough evaluation and provide meaningful feedback. Although any psychological or behavioral assessment should be multidimensional and include all relevant domains of function, the specific measures used and the areas of most intense focus will differ depending on the consultation question. For example, an assessment to inform a decision about appropriateness for surgical intervention would have a different focus than an assessment to determine appropriateness for psychological pain treatment.

Overview of the Psychological and Behavioral Assessment Process

Ideally, psychological and behavioral assessment of patients with chronic pain should follow a hypothesis generating and testing approach. The assessment should begin broadly; as problems are identified, the clinician can hypothesize contributing and maintaining mechanisms. The assessment process will be increasingly focused and behaviorally oriented as the hypothesized mechanisms are investigated. Generally, the assessment process begins with a standardized interview that assesses the pain complaint and

patients' physical, emotional, social, and occupational functioning. This allows for the assessment of patients' past and present levels of functioning and the temporal association of any changes in functioning to the pain complaint. Besides the information gained in the interview, questionnaires, diaries, behavioral observations, significant other reports, and medical record information may be used as adjunct sources of information. The use of multiple adjunct measures helps avoid the biases or error associated with reliance on a single assessment strategy. Hypotheses about the factors that initiated and maintain adjustment and functioning problems are generated and refined throughout the assessment process. Ultimately, the validity of hypotheses is tested by examining patients' response to treatment.

For example, anxiety and fear of pain have been shown to contribute to unfavorable outcomes for persons with chronic pain complaints.[5] Significant functional disability can be associated with fear of pain and further injury, such as behavioral avoidance, muscle deconditioning because of reduced activity, muscle hyperreactivity to stress, negative and distorted cognitions about the adverse effects of activity, and psychological distress secondary to restricted access to pleasant and rewarding activities. Thus when an initial interview provides evidence of a significant decline in physical functioning and anxiety is present as described above, it becomes a reasonable hypothesis and avenue for more targeted assessment through the use of specific questionnaires, diaries, or reports from significant others (e.g. spouses or partners) to determine the extent to which anxiety is present and interacting with the pain experience. Ultimately, the assessment process should result in a model that describes the patient's specific pain experience, explicates how that patient's beliefs, experiences, strengths, and weaknesses have resulted in their current level of functioning across domains and provide an individualized treatment plan that uses these hypotheses to target specific factors for intervention.

Domains of Functioning

The multidimensional nature of chronic pain necessitates a broad assessment of multiple domains of functioning to provide a valid snapshot of a patient's unique pain experience and meaningfully guide intervention strategies. A useful guide for the assessment process is the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group consensus statement regarding the core outcome domains that should be assessed and recommended instruments for measuring those domains when evaluating the efficacy of a pain treatment.[6–8]

Although originally generated to aid researchers in increasing comparability across randomized controlled studies of pain treatments, these recommendations can be useful to the clinician in guiding assessment. The IMMPACT group, which consists of recognized experts drawn from academia, government agencies, and the pharmaceutical industry, recommend assessing the following chronic pain domains: pain, physical functioning, emotional functioning, patient ratings of improvement and satisfaction with treatment, treatment-related symptoms, and adverse events, and patient disposition. Additionally, through literature review and expert consensus, the group has provided recommendations regarding specific assessment instruments within each domain applicable across various pain complaints. This same group has also developed recommendations for the future development of patient-oriented outcome measures that may provide a more sensitive and efficient assessment of the key outcome domains relevant to a comprehensive assessment of patients with pain.[8]

Overview of Assessment Strategies

Multiple assessment strategies such as interviews, standardized questionnaires, diaries, behavioral observation, psychophysiologic assessment, and assessment of family members and significant others are commonly used to investigate and quantify the pain experience and concomitant physical and emotional functioning. Multiple, standardized assessment measures are encouraged to obtain comprehensive, valid, and reliable information.

The well-conducted clinical interview can be a rich source of information regarding a patient's pain and pain treatment history as well as the resulting physical, emotional, behavioral, and cognitive responses.[9,10] The interview also provides an opportunity for clinicians to interact with a patient, to establish rapport, and to develop an impression of that patient's receptivity to rehabilitation and treatment efforts. Interviews may be standardized or unstandardized. Even when conducting an unstandardized interview, it is useful to systematically investigate a pre-specified set of domains. (Table 22.1 is an example of an interview structure used in the author's [RK] comprehensive pain management clinic.)

Questionnaires and inventories provide opportunities for focused assessment of specific domains of functioning and quantifying patient responses. Because published questionnaires have typically met standards for reliability and validity, greater confidence can be placed in the information provided by these measures. Questionnaires typically permit quantification of important dimensions of the experience of pain and allow for evaluation of within-person change over time. The concurrent administration of measures of multiple domains of functioning can assist in the identification of patient relative strengths and weaknesses across these domains, such as the identification of patients who report low levels of disability and distress despite an apparently severe level of pain intensity. Questionnaires with normative data offer the added benefit of providing a comparison point for evaluating the status of the respondent relative to others with similar painful conditions or within similar demographic (i.e. age, race/ethnicity, gender) groups. Ultimately, they may provide a more efficient and cost-effective option for more intensive and time consuming interviews. Following this brief overview of psychological and behavioral assessment strategies, several questionnaires and inventories frequently employed in assessing patients with pain in the clinical setting are reviewed.

Ecologic momentary assessment (EMA) is an umbrella term for measurement tools ranging from pen and paper diaries to smartphone apps and wearable technologies that sample biomarkers and physiologic parameters.[11] Across these different tools, EMA measures seek to measure behaviors, perceptions, and physiologic markers in real-world contexts and offer many advantages over other assessment methods. They allow for information about pain, sleep, and physical and emotional functioning to be recorded prospectively and once or more times a day, eliminating distortions associated with memory and retrospective recall.[12] EMA measures are also thought to increase the ecologic validity of assessments, as observations and ratings occur in patients' natural environment during real (vs. contrived) situations.[11] Additionally, EMA measures allow for recording the temporal association between pain and other factors. For example, many sleep diaries and smartphone applications collect information about pain intensity scores prior to sleep as well as sleep quality and duration.[13] This allows for the investigation of the relationship between pain and functioning instead of examining either factor in isolation. The composition of EMA measures can vary from those designed to assess a single

TABLE 22.1 Comprehensive Pain Interview

Demographics:

Age, gender, race/ethnicity, family/marital status.

Referral Source:

Referring MD and service, the reason for referral.

Behavioral Observations:

Noteworthy pain behaviors or behaviors indicative of psychiatric disturbance, otherwise, state "unremarkable."

Pain Complaints and Treatment History:

Please ask the patient the location of pain sites, then copy and paste questions one through seven for each pain site. If the patient describes a pain site as running through the leg, knee, and foot, check all sites below but evaluate as one pain site. Thus for the patient who identifies three pain sites: lower back, right hip and leg, and hands, record three pain sites here, then complete one to seven three times, each time identifying a different pain location "lower back," "hip and leg," and "hand." Qualify when necessary (e.g. left leg only, write this in).

1. LOCATION OF PAIN

[ ] head/face [ ] neck [ ] shoulder [ ] arm [ ] hands

[ ] stomach/abdomen [ ] upper back [ ] lower back [ ] hip [ ] leg

[ ] knee [ ] foot [ ] anal [ ] genital

[ ] whole body [ ] other sites (specify)

2. INTENSITY OF PAIN

The patient rates their average level of pain over the past week as follows:

0——1——2——3——4——5——6——7——8——9——10

No Worst Possible

Pain

Worst pain gets: Best pain gets: Average pain rating:

3. <u>QUALITY OF PAIN</u> (Do not prompt; use patient's own words when possible):

[ ] dull [ ] stabbing [ ] hot-burning [ ] shooting [ ] aching

[ ] piercing [ ] tingling [ ] numb [ ] squeezing [ ] throbbing

[ ] pulling [ ] sharp [ ] cramping [ ] gnawing [ ] heavy

[ ] tender [ ] radiating [ ] deep

[ ] other (specify)

4. ONSET/DURATION:

Approximate time pain started:

5. VARIATIONS/PATTERNS/RHYTHMS:

The pain is [ ] constant [ ] intermittent [ ] episodic/recurring

[ ] other (specify)

6. WHAT RELIEVES THE PAIN?

[ ] sitting [ ] lying down [ ] standing [ ] heat [ ] cold [ ] rest

[ ] distraction [ ] exercises [ ] movement

[ ] other (specify)

7. WHAT CAUSES OR INCREASES PAIN?

[ ] sitting [ ] lying down [ ] standing [ ] heat [ ] cold [ ] rest [ ] exercises

[ ] movement

[ ] other (specify)

Continued

TABLE 22.1 Comprehensive Pain Interview—cont'd

8. EFFECTS OF PAIN:

Other associated symptoms: [ ] nausea [ ] vomiting [ ] dyspnea

[ ] confusion [ ] weakness [ ] numbness

[ ] other (specify)

The pain affect the patient's

[ ] sleep [ ] movement [ ] energy

[ ] lifestyle [ ] personal relationships [ ] work [ ] emotions

[ ] concentration [ ] appetite [ ] motivation [ ] activities of daily living [ ] instrumental activities of daily living

[ ] other (specify)

9. PATIENT'S PAIN GOAL (check any appropriate boxes, if appropriate, add brief descriptors of patient goals regarding reduced level of pain intensity, goals related to function, ADLs, quality of life):

[ ] sleep comfortably [ ] comfort at rest [ ] comfort with movement

[ ] stay alert [ ] perform activity (specify)

[ ] other (specify)

Acceptable level of pain (0 – 10 scale):

10. PAIN MEDICATIONS (During the interview, determine current use, dosage, and general effectiveness of pain medications to determine the patient perception of effectiveness).

11. NON-PHARMACOLOGIC METHODS OF PAIN RELIEF AND EFFECTIVENESS: (For each method patient has used, note which pain sites involved, past or present use, and effectiveness [yes/no])

[ ] Physical Therapy

[ ] Surgical Interventions

[ ] Psychotherapy

[ ] Relaxation

[ ] Biofeedback

[ ] Manual Treatments

[ ] TENS

[ ] Heat Application

[ ] Cold Application

[ ] Occupational Therapy

[ ] Distraction

[ ] Exercises [ ] Stretching

[ ] Other (specify)

Relevant Medical History

Significant recent medical history.

Psychosocial History and Present Status:

Significant mental health and substance abuse history

Current employment status, current living arrangements

domain, such as pain intensity to those that are much more comprehensive and multidimensional. Patients may already engage in self-monitoring and recording and might be using pen and paper measures, smartphone applications, or a combination of modalities. It can be useful to ask patients about self-monitoring habits and consider the implantation of EMA technologies in routine patient assessment. The use of innovative technologies such as mobile telephone apps, web-based diaries, and interactive voice response systems are increasingly being promoted as more efficient strategies for the collection of prospective information.[14]

Advances in wearable technologies also provide an efficient and powerful strategy for collecting EMA data. Consumer grade devices (e.g. AppleWatch and FitBit) and research grade devices (e.g. SenseWear Armbands, Step-Watch 3) can measure a range of biometric data, including steps taken per day, heart rate, and duration and intensity of physical activity.[15] Steps taken per day, and other measures of physical activity and energy expenditure, can be particularly useful metrics to capture in patients with chronic pain, as reduced physical activity levels can cause worsening of comorbidities. Additionally, evidence suggests that routine physical activity can reduce pain severity and improve quality of life and physical functioning.[16] Subsequently, wearable technologies can provide both clinicians and patients with objective measures of important modifiable health behaviors.

Behavioral observation is a useful adjunctive to self-report. Although pain is a private, subjective experience, it is possible to observe signs that patients are experiencing pain by direct behavioral observation. Patients can communicate that they are experiencing pain and the intensity of the pain through facial expressions, crying, moaning, limping, guarding, and rubbing affected areas. Behavioral observation of patients with chronic pain can provide valuable adjunct information beyond that gathered using a self-report format and is crucial to the evaluation of patients with cognitive or physical limitations that interfere with verbal communication. Behavioral observation methods have been developed to assess patients with a range of painful medical conditions, including cancer pain,[17] rheumatoid arthritis,[18] osteoarthritis,[19] and low back pain.[20] Prkachin and his colleagues[21] reported on a method for assessment of pain behaviors in the context of a clinical evaluation of patients with low back pain. These methods have also been developed and used in studies of pain-relevant communication in partner dyads.[22] To obtain reliable and valid behavioral observation data, it is necessary to have a systematic plan for behavioral observation, coding, and interpretation of the data; thus the use of these methods requires considerable technological sophistication and expense.[23] The use of behavioral observation methods is commonly limited to the clinical research setting because of the time-intensive and costly nature of these methods.

The reports of families and significant others in the assessment of pain have been strongly encouraged in contemporary models of pain, particularly Fordyce's operant conditioning model,[24] and Turk's cognitive behavioral model,[25] which have specifically encouraged this focus given hypothesized roles of social contingencies in the perpetuation, if not etiology, of persistent pain and disability and the awareness of the frequent negative impact of persistent pain on significant others. In particular, the role of solicitousness in the development and maintenance of pain related disability has been a topic of a great deal of research. Operant principles specify that when spouses provide solicitous responses to pain behaviors, the pain behaviors are more likely to be emitted in the future, even in the absence of continued nociception. Positive or solicitous responses from spouses and family members, contingent on pain behaviors, may reinforce these maladaptive behaviors and encourage the development and maintenance of pain and pain related disability. Examples of solicitous behavior examined in the literature include expressions of sympathy or concern for the spouse, physical assistance or performance of a task, and encouraging rest and discouraging activity. In general, spouse solicitousness is significantly related to greater pain intensity, greater frequency of pain behaviors, higher levels of disability,[26–28] and increased help-seeking behaviors.[27,28] Distracting responses from significant others, meaning responses that are intended to cue engagement in other behaviors in an effort to distract from pain, have been found to be positively related to poor outcomes despite the likely intent of these responses to encourage adaptive coping with pain.[26] In addition to global measures of family and marital relationships, numerous questionnaires and inventories,[29–31] diaries,[32] and behavioral observation methods[22] have been developed specifically for the assessment of pain-relevant communication and the impact of pain on family members and significant others.

Psychophysical measures are primarily used to demonstrate the influence of psychological factors on the initiation and maintenance of pain symptoms.[33] For clinicians, psychophysical measures provide evidence that psychological factors are influencing biologic reactions in an individual patient and provide information regarding the utility of certain types of interventions (e.g. biofeedback). For patients, evidence that psychological factors are influencing physical responses related to pain can provide direct feedback regarding the successful use of behavioral strategies to manage a pain disorder and increase confidence to engage in these behavioral strategies.[34]

The most common clinical use of psychophysical measures in the treatment of pain primarily occurs during biofeedback treatments. Biofeedback treatments utilize psychophysical measures to train patients in voluntary modifications of bodily reactions through the provision of feedback of physiologic processes.[33] Surface electromyographic (EMG) recordings are the most widely used psychophysical measure in biofeedback for pain disorders because muscle tension is implicated in most musculoskeletal pain disorders. EMG readings typically target specific muscle groups associated with the patient's pain disorder (e.g. trapezius muscle for patients with upper back pain and the erector spinae muscle for patients with lower back pain). Additionally, abnormal blood flow is linked to several chronically painful conditions, including migraine headaches and Raynaud's disease. For these conditions, measures of blood flow and peripheral skin temperature (a proxy for peripheral circulation) can be used in biofeedback treatments.

In recent years, heart rate variability (HRV) has risen in prominence as a well validated psychophysical biofeedback measure. HRV, a measure of the duration of time between consecutive heartbeats, is an important indicator of autonomic nervous system functioning and reflects the balance in the parasympathetic and sympathetic nervous systems.[35–38] Increased HRV generally indicates more adaptive physiologic reactions to environmental stressors. However, it should be noted that pathologic abnormalities in the heart's conduction system can also increase HRV. Assuming healthy cardiac functioning, HRV provides a powerful biofeedback measure, especially for patients with chronic pain, as multiple chronic pain conditions including fibromyalgia, chronic lower back pain, and migraine have been associated with reduced HRV in the literature.[35,38,39] Preliminary pilot studies have suggested that HRV biofeedback is an effective biofeedback treatment for chronic pain.[35,38,40]

Specific Psychological and Behavioral Assessment Strategies

Standardized assessment instruments, often in the form of questionnaires or inventories, are frequently used in the assessment of patients with pain (Table 22.2). Questionnaires allow for a focused examination of a specific domain such as pain intensity,

TABLE 22.2 Overview of Assessment Measures

Measure	Domain	Measure Details	Advantage/Disadvantages
Numerical rating scale (NRS)[44,*]	Pain intensity	Single item, written or oral	Demonstrated validity, easy to administer, high completion rate; single item hinders reliability
Verbal rating scale (VRS)[44]		Collection of pain descriptors	Demonstrated validity, easy to administer, high completion rate; may be difficult for persons with poor command of English
Visual analog scale (VAS)[44]		10 cm line with descriptive endpoints	Demonstrated validity, easy to administer; more likely to be incomplete than NRS or VRS, and single item hinders reliability
McGill pain questionnaire (MPQ)[49,*]		Collection of pain descriptors. Also assesses the location of pain and exacerbating and ameliorating factors	Demonstrated validity; not consistently associated with pain intensity but more consistently associated with psychological distress
Brief pain inventory (BPI)[64,*]	Pain interference	32 items, short form has 15 items, ultra-brief version (PEG) has three items	Widely used, demonstrated validity and reliability, easy to administer, brief versions appropriate for multiple clinical settings; PEG has demonstrated good validity and is shorter and easier to administer
Graded chronic pain scale-revised (GCPS-R)[67]		Six item scale includes PEG	Short and easily interpretable, it provides clinically meaningful gradation of patients with chronic pain
West Haven-Yale multidimensional pain inventory (WHYMPI - interference scale)[68,*]	Psychosocial impact	52 items, assesses multiple domains	Demonstrated validity and reliability, useful with a variety of pain complaints, widely used; relatively high response burden, scoring time consuming
Pain disability index (PDI)[1]	Physical/social role function	49 items, assesses perceived disability in seven areas	Demonstrated validity and reliability, can identify specific areas of perceived disability; relatively high response burden, scoring time consuming
Patient-reported outcomes measurement information system (PROMIS pain interference and pain behaviors item banks)[79,80]		Item banks (Interference = 41 items; Behaviors = 39 items)	Standardized bank of items developed by National Institutes of Health (NIH), demonstrated reliability and initial validity, available in short forms; good demonstrated validity and reliability
Sickness impact scale (SIP)[89]		136 items and 24 items brief version for persons with chronic back pain	Demonstrated validity and reliability, responsive to change; full version has high response burden
Minnesota multiphasic personality inventory 2 - restructured form (MMPI-2-RF)[92]	Personality	567 true-false items	Most widely used personality measure, uses normative data in scoring; high response burden, difficult to score, requires training to interpret, restructured clinical scales have demonstrably improved discriminant validity in patients with chronic pain
Millon behavioral health inventory (MBHI)[97]		150 true-false items	Developed specifically for use with persons with medical conditions, demonstrated validity and reliability; high response burden, scoring time consuming, not predictive of outcomes in treatment studies of persons with chronic pain
Beck depression inventory (BDI)[101,*]	Emotional function	21 items, measures depression	Demonstrated reliability and reliability, sensitive to change; somatic items may be associated with pain rather than mood, a possible bias for certain populations
Center for Epidemiological Studies depression scale (CES-D)[110]		20 items, measures depression	Demonstrated reliability and validity in a wide variety of ethnic populations, non-English version available; lacks sensitivity and specificity without psychiatric interview
Geriatric depression scale (GDS)[118]		30 yes-no questions, measures depression in older adults	Demonstrated reliability and validity, good sensitivity and specificity; has not yet been widely used in chronic pain samples

TABLE 22.2 Overview of Assessment Measures—cont'd

Measure	Domain	Measure Details	Advantage/Disadvantages
Patient health questionnaire-9 (PHQ-9)[121]		Nine items, measures depression	Demonstrated reliability and validity across multiple populations, translated into several languages; does not specifically assess for mania and therefore underdiagnoses bipolar disorder
General anxiety disorder-7 (GAD-7)[126]		Seven items, measures generalized anxiety	Demonstrated validity and reliability in patients with chronic pain, easy to use, assesses for anxiety-related interference
Beck anxiety inventory (BAI)[129]		21 items, assesses anxiety symptoms	Good validity and reliability, normed on multiple clinical populations and translated into several languages, provides an indication of anxiety symptom severity
Pain anxiety symptom scale (PASS)[137]		53 items, assesses pain related fear	Demonstrated validity; poor prediction of pain related disability, relatively high response burden
Spielberger state-trait anxiety Inventory (STAI)[141]		Two 20 item measures of state and trait anxiety	Acceptable psychometric properties, widely used, sensitive to change
Medical outcomes study short form health survey (SF-36)[144]		36 item measure of perceived physical and emotional health	Psychometrically sound, widely used; concerns regarding measure's sensitivity and validity in discriminating dimensions of functional limitations in patients with pain
Survey of pain attitudes (SOPA)[154]	Pain beliefs and coping	57 item measure of pain related beliefs, brief forms are also available	Psychometrically sound, scores correlated with treatment outcomes and physical and emotional functioning
Pain stages of change questionnaire (PSOCQ)[161]		30 item measure of readiness to change	Demonstrated reliability and validity, predicts completion of treatment, changes in PSOCQ predict changes in "readiness"; may not be predictive of treatment outcomes
Chronic pain coping inventory (CPCI)[168]		64 item measure to assess the use of pain coping strategies	Psychometrically sound, patient coping strategies found to be associated with outcomes; high response burden
Pain catastrophizing scale (PCS)[172]		13 item measure of pain related catastrophic thoughts	Psychometrically sound, associated with treatment outcomes, demonstrated reliability and validity across different clinical populations, translated into several languages; further evaluation across racial groups is warranted
Chronic pain acceptance questionnaire (CPAQ)[188]		20 item measure of pain acceptance; eight item brief form also available	Demonstrated reliability and cross-sectional validity; associated with treatment outcomes, measure is specific to a single type of pain treatment, and further information regarding predictive validity is warranted
Revised American Pain Society pain outcomes questionnaire (APS-POQ-R)[199]	Quality of care	12 item measure of perceived quality of pain treatment	Commissioned by the American Pain Society and demonstrated reliability and internal validity

* = Measure was selected by the IMMPACT panel as the preferred measure within a domain.

pain interference, or coping beliefs and provide quantitative data that can be used to understand the patient's functioning relative to the general population or other patients experiencing pain.

Pain Intensity

Historically, change in pain intensity from baseline to posttreatment has been the primary outcome measure used in evaluating the efficacy of a given pain treatment.[41] However, pain intensity should not be used as a primary, unitary pain outcome measure as it does not directly correlate with pain related disability, and its measurement does not improve the quality of patient pain management.[42, 43] This section briefly outlines pain intensity measures. However, clinicians should not consider these to be sufficient nor comprehensive assessment measures of pain in patients.

Measures that attempt to quantify the private experience of perceived pain intensity include the numeric rating scale (NRS), the verbal rating scale (VRS), and the visual analog scale (VAS).[44]

The NRS is a single item rating scale of pain intensity that can be administered in an oral or written format. Patients are asked to specify their pain on a scale of zero to ten, with zero representing "no pain" and ten representing "the worst pain imaginable" The ease of administration and scoring advantage the NRS.[44,45] The VRS contains a list of pain descriptors that typically range in intensity from "No pain" to "Severe pain." Patients select the descriptor that best characterizes their level of pain. The descriptors are then assigned a numeric value based on intensity level (i.e. no pain = zero, mild = one, moderate = two, and severe = three).[44] While the VRS is easy to administer, patients with limited vocabularies or command of English may have difficulty discriminating among the descriptor words.[44] The VAS uses a 10 cm long line with endpoints denoting the absence of pain (e.g. "no pain") at one end and extreme pain at the other: Respondents mark the point that best characterizes their pain intensity, and a score is calculated based on the distance from the "no pain" endpoint to the respondent's mark. Electronic administration of the VAS has been found to have good psychometric validity and reliability than pen and paper administration.[46–48] However, depending on the electronic administration modality, anchoring bias must be considered when evaluating responses. Selection of the anchor (where the mark initially appears on the scale, e.g. at zero or five) may unintentionally bias pain reporting toward that anchor.

The McGill pain questionnaire (MPQ)[49] is a lengthier measure designed to assess the quality and affective component of the pain experience, not simply pain intensity. Respondents choose pain descriptors from a list of 78 potential descriptors that fall into 20 pain categories. These descriptors assess four pain domains: sensory, affective, evaluative, and miscellaneous. Within each category, the individual descriptors reflect varying degrees of intensity and are assigned corresponding numeric values that reflect this difference. Respondents also highlight the location of their pain on a figure drawing and provide information about the factors that alleviate and aggravate their pain intensity. The MPQ generates three scores: 1) the pain rating index, which is the sum of all words chosen in the available categories (the sum of the value of each subclass can also be obtained; 2) number of words chosen, a score that reflects the number of words chosen from each of the four categories; and 3) the present pain intensity, a rating of current pain on a scale from zero (no pain) to five (excruciating).[23] The MPQ has been widely used in a variety of pain focused research and has been validated in several other languages.[50–54] A 15 item short version of the MPQ (SF-MPQ) is also available.[55] The MPQ has demonstrated validity across various criteria, including pain intensity, perceived quality of life, ability to discriminate among pain conditions, pain medication use, and sensitivity to the effects of pain treatment.[56,57] The SF-MPQ demonstrated high correlations with the pain rating indices of the MPQ and was sensitive to change produced by pain medications in patients with pain.[58,59] Furthermore, the SF-MPQ2 includes an NRS, which allows for evaluating both the quality and intensity of the pain experience.[60,61]

Pain Interference

Pain intensity is an insufficient measure of pain, and there has been a strong trend toward focusing on the constructs of pain related functioning and the ability to attain personally valued and meaningful behavioral goals as treatment foci.[42] In line with this, providers are encouraged to assess patients for high impact chronic pain (HICP)—pain at least most days for ≥3 months with ≥1 activity limitation/participation restriction.[42] Patients with HICP experience more severe effects of pain across multiple domains, and experience more psychiatric diagnoses, cognitive impairment, difficulty with self-care, increased healthcare utilization, and worse overall health than patients reporting chronic pain without limitations. Subsequently, this diagnosis provides clinicians with a useful indication of pain severity and expected morbidity. Patients can be assessed for HICP with the question, "over the past six months, how often did pain limit your life or work activities? Would you say never, some days, most days, or every day?"[62,63] Patients reporting pain-related limitations most days or every day meet criteria for HICP.

Additional measures of pain interference include the brief pain inventory (BPI), the pain, enjoyment of life, and general activity scale (PEG), graded chronic pain scale–revised (GCPS-R), West Haven-Yale multidimensional pain inventory (WHYMPI), pain disability index (PDI), patient-reported outcomes measurement information system pain interference and behaviors (PROMIS pain interference and pain behaviors), and sickness impact profile (SIP).

The brief pain inventory (BPI)[64] was initially developed to measure pain intensity and interference in patients with cancer pain, but it has been widely used to assess non-cancer pain. A short form of the BPI containing 15 items is also available. The short form of the BPI has been found to have high internal consistency scores ranging from 0.82 to 0.95 for the Severity and Interference scales in a sample of patients with arthritis and lower back pain.[65] Demonstrations of its reliability and validity and its availability in multiple languages have contributed to it being recommended by IMMPACT to measure physical functioning in pain clinical trials.[6] The PEG is an ultra-brief version of the BPI consisting of three items: (P) pain intensity, (E) enjoyment of life, and (G) general activity. Development studies demonstrated reliability and validity for the PEG comparable to that of the longer BPI.[66]

The graded chronic pain scale-revised (GCPS-R) can also be used to distinguish between high impact chronic pain (grade three), bothersome chronic pain (grade two), and mild chronic pain (grade one).[67] The six item scale assesses for chronic pain, HICP, and inability to work because of pain and includes the PEG (pain, enjoyment, and general activity) scale. The measure is short and easily interpretable for both patients and clinicians. Unlike other measures of pain related interference, the GCPS-R provides a clinically meaningful gradation of patients with chronic pain, with analysis finding statistically significant differences in adverse health statuses (i.e. pain coping beliefs, affective disorders, activity limitation, and the likelihood of receiving long-term opioid therapy) between the different groups.[67]

The West Haven-Yale multidimensional pain inventory (WHYMPI)[68] is designed to measure psychosocial and behavioral aspects of chronic pain and is useful across various pain complaints. It is a 52 item multidimensional self-report instrument that employs seven point Likert scales. The instrument consists of three sections. Section one includes six scales measuring pain related interference across several domains, including work and leisure activities as well as interpersonal relationships, perceived support from a spouse or significant other, pain severity and suffering, perceived life control, and negative mood. Section two assesses the patient perception of significant others' responses to overt expressions of pain, classifying responses as solicitous, distracting, or negative. Section three measures the frequency with which the patient engages in four clusters of everyday activities, including household chores, social activities, outdoor work, and

activities away from home. The WHYMPI takes approximately 10 to 15 min to complete and is written at a fifth grade reading level. Test-retest reliability over two weeks ranges from 0.62 to 0.91, and internal reliability coefficients range from 0.70 to 0.90.[68] Several investigative teams have generally replicated the factor structure and psychometric properties of the WHYMPI.[69] Turk and colleagues have proposed an empirically derived taxonomy of the WHYMPI that includes three reliable profiles of patients with persistent pain labeled as dysfunctional, interpersonally distressed, and adaptive copers,[70] and these investigators and several other groups have replicated these findings in numerous samples of patients with various pain conditions.[71] The measure has been used in numerous empirical studies, including clinical trials of psychological and pharmacologic interventions, studies of the psychosocial impact of pain, and studies examining the role of psychosocial factors as contributors to the development and maintenance of persistent pain. The IMMPACT group recommended using the interference scale of the WHYMPI for use as an outcome measure in pain clinical trials.[6] The second section of the measure that focuses on significant other responses has been particularly valuable in evaluating the role of such responses as predictors of severity of pain and pain related disability and distress.[72]

Three additions to the original version of the scale have enhanced its overall reliability, validity, and clinical utility. Rudy[73] added two items to the life control and interference scales, Okifuji and her colleagues[74] proposed alternative instructions for the significant other response section to reduce missing observations, and Bruehl and colleagues[75] developed a scale to detect random responding and malingering. A version using significant others as the reporters has also been published.[29]

The pain disability index (PDI)[1] is a brief measure of pain related interference with role functioning. The PDI includes seven items assessing perceived disability in each of seven areas of functioning: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity. Each item is rated on a ten point Likert scale (zero = no disability to ten = worst disability). The PDI has demonstrated internal consistency values of 0.85 to 0.86 and excellent test-retest reliability.[76] Validity has been demonstrated through its association with the Oswestry disability questionnaire (focused specifically on chronic lower back pain),[77] physical functioning tests,[78] and measures of pain intensity.[77]

The National Institutes of Health (NIH) PROMIS is a standardized item bank developed by a cooperative group for the purpose of developing psychometrically sound standardized measures to assess patient-reported outcomes. These measures provide information in the domains of physical, mental, and social health across a variety of medical illnesses. Measures for pain currently available in the PROMIS assessment center (www.healthmeasures.net) include the general measures of pain interference and pain behaviors and more specific measures of neuropathic pain quality.[79] The pain interference item bank includes 41 items, with four short forms consisting of four to eight items.[80] The pain behaviors item bank includes 39 items with a single short form consisting of seven items.[81] Both measures demonstrated reliability and validity in psychometric evaluation, were related to other measures of pain related outcomes, and discriminated among groups of patients with differing self-reported health, numbers of chronic conditions, and numbers of disabling conditions. Further studies have demonstrated that the pain related measures and global scores of quality of life are higher in clinical pain samples than samples from the general population.[82] Extant research has found the PROMIS pain interference and pain behaviors scales to provide comprehensive, sophisticated, and psychometrically sound measures for pain related patient-reported outcomes: the measures have been translated into other languages and have been found to be reliable and valid.[83–85] Recently, measures of pain interference and behavior have also been developed specifically for use with pediatric patients,[86–88] and their parents,[87] but there is a small body of existing literature on the reliability and validity of these measures.

The sickness impact profile (SIP)[89] measures the degree of disability across 12 domains of functioning. One hundred and 36 items are used to derive measures of sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication. These domain scores are combined to produce physical, psychosocial, and total disability scores. The SIP can be self-administered or administered by an interviewer in about 20 to 30 min.

An extensive period of development and testing and reports on these efforts support the reliability and validity of the measure. It has been found to be responsive to change during treatment for chronic pain.[90] A brief version, called the Roland Morris disability questionnaire, consisting of 24 items, has been developed specifically for use with patients with chronic low back pain.[91] This measure has also been shown to have strong evidence of reliability, validity, and responsiveness to change as a function of psychological interventions and is recommended by IMMPACT[6] as the preferred measure of physical functioning for evaluating persons with back pain.

Personality

The Minnesota multiphasic personality inventory (MMPI)[92] is the most commonly employed evaluative measure for the psychological functioning of patients with pain. The MMPI-2-RF is comprised of 338 true-false items used to derive scores on three higher-order scales, and nine restructured clinical scales, eight validity scales, 14 somatic/cognitive and internalizing scales, 11 externalizing, interpersonal, and interest scales, and the personality psychopathology five scales.[92] The MMPI-2-RF was normed on a representative sample of the United States population, and the restructured clinical scales have demonstrated validity in predicting psychopathology. Earlier versions of the MMPI (MMPI or MMPI-2) were considered inappropriate for assessing patients with chronic pain, owing to psychometric limitations that caused clinical scales to reflect disease status rather than psychological functioning.[93,94] The MMPI-2-RF's restructured clinical (RC) scales were developed to address psychometric and theoretical limitations of the earlier MMPIs, and the RC scales have demonstrably improved discriminant validity in patients with chronic pain.[95,96]

The Millon behavioral health inventory (MBHI)[97] was developed to assess the psychological functioning of patients with medical conditions. This 150 item measure contains eight scales designed to assess the respondent's interaction style (e.g. cooperation), six scales that assess the respondent's response to illness (e.g. pain treatment responsivity), and six scales that assess the presence of psychosocial stressors (e.g. social alienation). Questions are posed in a true/false format. Respondent's answers are scored by comparison with the base rate in the normative sample, which consisted of patients with various medical illnesses.

The MBHI has been demonstrated to have substantial reliability and validity indices. It may have advantages relative to

the MMPI-2-RF for use in the assessment of patients with pain conditions as a function of its relative brevity and the fact that it was developed and normed on medical, as opposed to psychiatric, populations. However, to date, studies have failed to demonstrate the predictive validity of the MBHI in studies of psychological interventions,[98] surgical interventions,[99] or multi-disciplinary treatment of patients with chronic pain.[100]

Emotional Functioning

Assessment of the emotional functioning of patients experiencing chronic pain should be conducted in the context of any pain-relevant intervention. The high prevalence of emotional distress among patients with chronic pain conditions, the negative effects of emotional distress on pain and pain related disability, the inflated healthcare costs associated with emotional distress among patients with chronic pain, and the influence of emotional distress on pain treatment participation provides the rationale for this recommendation.[6] The following brief review considers just a few of the many standardized measures of depressive symptom severity, anxiety, and anger, the three most commonly cited and studied emotional concomitants of the experience of persistent pain.

The Beck depression inventory (BDI) was developed to measure the behavioral manifestations of depression in adolescents and adults and standardize the assessment of depressive symptom severity to monitor change over time.[101] In its original form, the BDI consisted of 21 groups of four to five statements describing symptoms in each cluster from low to high. Respondents were instructed to endorse the single item in each group that best describes how they were feeling "right now." The original version was designed to be used in an interview format, but subsequent versions have more commonly been used in a self-report questionnaire format. In 1978 the full scale was revised to eliminate redundancy among some of the items, and the time frame for assessment was altered to "during the last week, including today." Only four possible responses for each symptom cluster are now included so that scores on the measure range from 0 to 63. In 1996, the BDI-II was published and included revisions to some items and the time frame for assessment to be consistent with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Although the BDI-II has advantages in terms of the content of the items and consistency with current diagnostic nomenclature, concerns have been raised about its sensitivity to change during brief periods.[102] The 21 item version of the BDI takes about 5 to 10 min to complete.

The reliability and several dimensions of validity of the measure have been extensively reported. In a review of 25 years of research with the BDI, Beck and colleagues reported on 25 studies that reported on the internal consistency of the measure.[103] Across psychiatric, healthy, and medically ill samples, indices of internal consistency (alphas) ranged from 0.73 to 0.95. Stability estimates (i.e. test-retest correlations) have consistently been high as well, typically varying in the 0.80 to 0.90 range depending on the assessment interval and sample. Validity estimates for psychiatric patients have been assessed by examining the correlation between BDI scores and clinical ratings of depression (e.g. using the Hamilton rating scale for depression) average of about 0.72. For nonpsychiatric patients, the average validity estimate is 0.60. In a review of eight studies of sensitivity to change, Moran and Lambert[104] found that the BDI was sensitive to change as a function of psychotherapy and pharmacotherapy outcome studies. Some evidence suggests a reporting bias for certain populations, including women, adolescents, and elderly persons, although the robustness of these observations is not clear.

The BDI has been used extensively in studies designed to evaluate the efficacy of pharmacologic and nonpharmacologic treatments for chronic pain,[105–109] and there is ample evidence of its sensitivity to change. Results of most studies provide compelling support for the use of the BDI in assessing improvements in depressive symptom severity as a function of pain treatment, and it has been recommended as one of the core outcome measures for assessment in pain clinical trials.[6]

The Center for Epidemiologic Studies depression scale (CES-D) was developed to screen for the presence of depressive illness and to measure levels of symptoms of depression in community samples.[110] The scale's 20 items were selected from existing scales (e.g. BDI, MMPI depression scale, Zung self-rating depression scale) to represent the major components of depression based on clinical and empirical studies. Respondents are asked to rate the frequency of a given symptom on a zero (rarely or none of the time) to three (most or all of the time) scale with reference to the past week. Four items are worded in the positive direction to partially control for response bias. The CES-D takes about 5 min to complete.

Indices of internal consistency (Cronbach's alpha) have been reported to be 0.85 for community samples and 0.90 for psychiatric samples. Split-half reliabilities are also high, ranging from 0.77 to 0.92. Test-retest correlations over a six to eight week period range from 0.51 to 0.67.[110] Roberts[111] reported that studies of African American and Mexican-American respondents revealed similar reliability estimates. The reliability and validity of the measure have also been examined in numerous ethnic populations, and it has been translated into several languages.[110] Overall, high levels of internal consistency have been reported across numerous samples from the general population and patient samples, irrespective of age, gender, race, and geographic location. In a sample of chronic pain patients, the level of internal consistency was found to be 0.90.[112] Indices of criterion-related validity have generally been reported to be moderate to high. For example, correlations between the CES-D and the depression scale of the SCL-90 for samples of psychiatric patients have been reported to range from 0.73 to 0.90. Correlations with the Hamilton rating scale for depression for similar samples have ranged from 0.49 to 0.85. Studies of elderly samples have revealed somewhat lower validity estimates.

Investigators have challenged the diagnostic sensitivity of the CES-D.[113,114] Investigators in the pain field have called for modifications of the measure in terms of item content[115] or scale cutoffs for the diagnosis of depression.[114,115] Ultimately, it is fair to say that the measure lacks the sensitivity and specificity for supporting its use in clinical diagnosis without concurrent use of a psychiatric interview. The CES-D has increasingly been used for the assessment of outcome following pain interventions, and in numerous cases, the measure has been demonstrated to be sensitive to change.[116,117]

The geriatric depression scale (GDS)[118] was specifically developed to assess depressive symptom severity among older patients and was encouraged by observations that all of the other self-report measures of the construct were developed and validated with medically healthy younger adults. These measures suffer from the criticism that they include numerous somatic symptoms common among non-depressed older adult patients and that their format for responding may be difficult for some older patients.

The GDS consists of 30 "yes" versus "no" questions; 10 are negatively keyed, and 20 are positively keyed. Questions are ordered

with more "acceptable" items presented first. A 15 item short form is also available.[119]

In the original publication, indices of internal consistency (0.94) and split-half reliability (0.94) were extremely high.[118] The GDS demonstrated high correlations with other measures of depression and was successful in discriminating mild from severely depressed groups in this same study and depressed older patients with arthritis from non-depressed patients with arthritis. Brink and colleagues[120] reported a high degree of sensitivity and specificity in discriminating depressed from non-depressed patients in a separate sample.

This measure seems to have substantial advantages for the assessment of depressive symptom severity among older adult patients. However, additional research with chronic pain samples will be necessary before its use in pain treatment outcome research can be supported.

The patient health questionnaire depression module (PHQ-9) is a self-administered diagnostic questionnaire that assesses for the presence of Major Depressive Disorder (MDD), based on the criteria set forth by the diagnostic and statistical manual (DSM-IV).[121] The PHQ-9 lists the nine DSM-IV depressive symptoms and asks how often the person has experienced the symptoms over the past two weeks: response options range from zero (not at all) to three (nearly every day). At the end of the screener, a separate question assesses the extent to which these symptoms have interfered with day-to-day life. Severity scores on the PHQ-9 can range from 0-27; higher scores indicate increased depression severity and are associated with measures of health-related quality of life.[121,122] The PHQ-9's reliability and validity have been examined across multiple care contexts, clinical populations, and racial and ethnic groups, and it has been translated into several languages.[123,124] Overall, the PHQ-9 has been found to have good internal reliability in primary care samples (Cronbach's alpha = 0.89), obstetrics and gynecology patients (Cronbach's alpha = −0.86), and patients with migraine (Cronbach's alpha = 0.89). In initial validation, test-retest correlation over a 48 h period was 0.84.[121,125]

Before making a final diagnosis, the provider should assess for and rule out physical causes of depression, current bereavement, and/or a history of a manic episode. A diagnosis of MDD is appropriate if the patient endorses experiencing five or more symptoms more than half of the days, with one of the symptoms being either depressed mood or anhedonia. If the patient endorses depressed mood or anhedonia more than half the days and one other depressive symptom, then the patient meets the criteria for "other depression."[121] For diagnostic purposes, endorsement of suicidal ideation (item nine) of any frequency (> zero) counts as a symptom and clinically indicates the need for further suicide risk assessment and safety planning with the patient.

The GAD-7 is a self-administered seven item screening measure for generalized anxiety disorder (GAD). The items assess the frequency of physiologic and cognitive anxiety symptoms in the past two weeks, and response options range in frequency from zero (not at all) to three (nearly every day). A final question assesses if these problems have interfered with daily activities.[126] The GAD-7 was initially validated on primary care patients and was found to have excellent internal consistency (Cronbach's alpha = 0.92), test-retest reliability (intraclass correlation = 0.83), and validity with established anxiety screening measures (intraclass correlation = 0.83).[126] The GAD-7 has also been found to be valid and reliable in the general population,[127] and patients with pain.[128]

The Beck anxiety inventory (BAI) is a 21 item self-report questionnaire that assesses the severity of anxiety symptoms, with items asking how much the symptoms bothered the respondent in the last two weeks from zero (not at all) to three (severely - it bothered me a lot). The measure focuses on the somatic symptoms of anxiety and was developed to discriminate anxiety disorders from depressive disorders, although it should not be used as a solo differential diagnostic tool.[129] The summed score of response options can be interpreted using the following ranges: 0 to 7 minimal anxiety, 8 to 15 mild anxiety, 16 to 25 moderate anxiety, and 26 to 63 severe anxiety, with a score greater or equal to 16 indicating clinically significant anxiety.[130,131]

The BAI was initially validated on psychiatric patients with anxiety and depressive disorders and was found to have high internal consistency (Cronbach's alpha = 0.92) and good test-retest reliability over one week (r = 0.75). The BAI's reliability and validity have been examined across multiple care contexts, clinical populations, and racial and ethnic groups, and it has been translated into several languages.[130,132–136]

The pain anxiety symptom scale (PASS)[137] was designed to assess the cognitive, physiologic, and behavioral domains of pain related fear. It includes 53 items distributed across four subscales measuring fear of pain, cognitive anxiety, somatic anxiety, and escape and avoidance. Respondents use zero (never) to six (always) scales to endorse the frequency of each of the symptoms. The PASS has been demonstrated to have adequate internal consistency,[137] with indices of internal consistency ranging from 0.81 to 0.89 for each of the four scales and 0.94 for the total scale. Good predictive validity,[138] and acceptable criterion validity have also been demonstrated.[139] The PASS has been criticized for its poor prediction of disability relative to other pain related fear measures,[139] and its factor structure has also been challenged.[140]

The Spielberger state-trait anxiety inventory (STAI)[141] was designed to identify and quantify both situational anxiety (state) and dispositional anxiety (trait). The STAI consists of two 20 item self-report inventories of each of these constructs. Respondents rate the degree of agreement to brief statements (e.g. "I feel calm") on four point scales ranging from "not at all" to "very much so" in terms of both their present state (state version) and their frequency over time (trait version). There is a high concordance between pain and anxiety as measured by the STAI,[142] and it has been widely used in the pain literature. It has acceptable psychometric properties,[139,141] and it is sensitive to change in anxiety as a function of pain treatment.[143]

The medical outcomes study short form health survey (SF-36)[144] was developed as a general measure of perceived health status and is typically self-administered. The measure contains 36 items combined to form eight scales: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. Respondents use "yes-no" or five or six point scales to endorse the presence or degree of specific symptoms, problems, and concerns. Scores on the scales range from 0 to 100, with higher scores indicating better health status and functioning. The measure takes about 10 to 15 min to complete. The SF-36 has been extensively validated with large samples from the general population and across several demographic subgroups, including samples of healthy persons over 65.[145]

Estimates of internal consistency (alphas) for most samples range from 0.62 to 0.94 for the subscales, with most estimates ranging over 0.80. Test-retest coefficients ranged from 0.43 to 0.81 for six months and from 0.60 to 0.81 for two weeks.[146] The SF-36 has been shown to correlate reasonably well with other criterion measures, measures of ability to work, utilization of healthcare

resources, and other clinically meaningful criteria such as "burden of care."[145–148] Factor analytic studies have supported the presence of two distinct factors labeled physical health and mental health functioning that account for 82% of the measure's variance.[148–150]

In one multi-site trial of cognitive-behavior therapy, exercise, and their combination, for patients with Gulf War Illness that included chronic, diffuse musculoskeletal pain as a primary feature, each of these treatments was found to be associated with improvements in the mental health functioning component score.[151] On a more negative note, Rogers and his colleagues reported that the SF-36 lacked reliability for the assessment of outcomes following multi-disciplinary pain treatment, and they questioned aspects of the measure's validity in discriminating dimensions of functional limitations.[152] Similar concerns about the sensitivity of the SF-36 to change have also been raised.[153] Continued examination of the sensitivity of the SF-36 Mental Health Functioning component to change as a function of pain interventions is indicated.

Pain Beliefs and Coping

The survey of pain attitudes (SOPA)[154] was developed to measure beliefs about chronic pain. It included five domains: perceived ability to control pain (control), perceived level of pain related disability (disability), belief in medical cures for pain (medical cures), belief that others should be solicitous toward them when they are in pain (solicitude), and the importance of medication as a treatment for pain (medication). The measure was later expanded to include two new dimensions: belief in the influence of emotions on pain (emotions) and belief that pain indicates underlying physical damage that necessitates the limiting of physical activity (harm).[155, 156] The final version of the SOPA has 57 items and employs a zero (this is very untrue for me) to four (this is very true for me) response scale. The SOPA is grounded in cognitive behavioral theory, which specifies that patients' beliefs about their pain influence important pain related outcomes, including emotional and physical functioning. A 30 item brief form of the SOPA (the SOPA-B)[157] and a 35 item short version (SOPA-R)[158] are also available.

Internal consistency alphas for the 57 item SOPA scales are good, ranging from 0.71 (control) to 0.81 (disability), and test-retest stability ranged from 0.63 to 0.68.[156] The shorter version of the SOPA, the SOPA-B, has demonstrated a seven-factor structure consistent with the original measure, adequate internal consistency (ranging from 0.56 ([medication] to 0.83 [solicitude]), and strong correlations with the corresponding SOPA scales (0.79–0.97).[157] The original factor structure of the SOPA-R has largely been confirmed by other investigators, and the measure has demonstrated good internal consistency (0.65–0.84) except for the medication scale (0.49).[159]

The main strength of the various versions of the SOPA is their correlation with clinical treatment outcomes. The disability scale of the SOPA (the belief that one is disabled) has demonstrated significant correlations with physical and emotional functioning.[156,159,160] The harm scale showed significant association with reported physical disability, and the medication scale was associated with treatment utilization.[156]

The most frequently used measure of the construct of "pain readiness to change" is the pain stages of change questionnaire (PSOCQ).[161] The PSOCQ measures beliefs about the degree of patient personal responsibility for pain control and interest in making behavioral changes to cope with pain. The PSOCQ is a 30 item self-report measure composed of four distinct scales. The precontemplation scale measures the degree to which a patient endorses little personal responsibility for pain control and no interest in making behavioral changes. Contemplation represents an increasing recognition of personal responsibility for pain control and interest in behavioral changes that support pain management. The action scale measures the extent to which patients believe that they are actively learning pain management skills. The maintenance scale quantifies patients' degree of commitment to using self-management strategies in their daily life and a high degree of personal responsibility for pain management.

A review of the empiric literature documents the reliability, and criterion, and concurrent validity of the measure.[162] Internal consistencies of the four scales range from 0.77 to 0.86, and stability indices range from 0.74 to 0.88. However, the utility of the PSOCQ hinges on its ability to predict important treatment process variables. Thus far, research has been encouraging. For example, PSOCQ subscales (i.e. precontemplation, contemplation, action, and maintenance) predict completion of self-management treatment programs,[163] and improvements in pain coping during treatment.[164] Furthermore, changes in PSOCQ during treatment consistent with increased readiness to change or "forward stage movement" are associated with improvements in pain and physical and emotional functioning.[163–166] However, the readiness to change model has not been without critics. For example, Strong and colleagues[167] challenged the external validity of the PSOCQ and demonstrated that a measure of self-efficacy had greater predictive validity than the PSOCQ.

The chronic pain coping inventory (CPCI)[168] is a 64 item questionnaire designed to assess patients' use of pain coping strategies. The questions contained in the scale fall into three broad categories and include eight subscales: wellness-focused or positive coping strategies (exercise, relaxation, task persistence, coping self-statements), illness-focused or negative coping strategies (guarding, asking for assistance, resting), and neutral coping strategies (seeking social support). Respondents report the number of days in the last week that they used each strategy.

The CPCI subscales demonstrated good internal consistency (0.74–0.91) and test-retest reliability (0.65–0.90).[168] Spouse report of patient disability and coping skill use was strongly associated with CPCI scales.[168] Other studies have largely confirmed the initially specified eight-subscale factor structure.[169,170]

Studies have found various associations between CPCI subscales and patient adjustment and outcomes. However, overall, illness-focused coping strategies were found to be significantly associated with poorer patient adjustment and outcomes, and wellness-focused strategies were significantly associated with better patient adjustment and outcomes.[169,171] An exception is relaxation, with some studies showing a counterintuitive association between relaxation and higher affective distress and lower pain control,[169,171] and another showing no associations between relaxation and any patient adjustment or outcome variable examined.[170] Importantly, even after controlling for pain severity and demographic factors, CPCI subscales were significant predictors of patient-reported physical functioning, mood, disability, and activity level.[170] A six month longitudinal study of patients with low back pain following a work accident demonstrated that higher guarding scores were predictive of prolonged leave from work.[171]

The pain catastrophizing scale (PCS) is a 13 item scale designed to measure the extent to which patients engage in catastrophic thinking regarding their pain.[172] Catastrophic thinking is characterized by thoughts that the pain is horrible, unbearable, and that the worst possible outcome of the patient's pain will manifest.

Patients record the frequency with which they experience thoughts and feelings described by items on a five point Likert-type scale ranging from zero (not at all) to four (all the time).

Initial scale development occurred in an undergraduate sample.[172] However, the PCS has demonstrated reliability and validity in both non-clinical and clinical samples. Factor analyses tend to identify three subscales: magnification, rumination, and helplessness.[172–175] These factors have demonstrated gender invariance.[174] However, evidence from a single study suggests that, particularly for African Americans, two subscales of rumination and magnification/helplessness might be more appropriate.[176] Internal consistency coefficients range from 0.60 to 0.91 for subscales and from 0.87 to 0.95 for the full scale.[172–175] The PCS has demonstrated validity through its association with catastrophic thought patterns identified through clinical interview,[172] pain severity,[173,175,176] pain interference,[173] pain related disability,[176] and mood and anxiety symptoms.[173] Further, the PCS has demonstrated discriminant validity from affect,[175] and psychological disturbance.[173]

The PCS has demonstrated responsiveness to cognitive behavioral and physical activity pain treatments and is considered an important mechanism of changes in these treatments.[177–181] The PCS has also been translated into several languages.[182–187]

The chronic pain acceptance questionnaire (CPAQ) is a 20 item scale designed to measure chronic pain acceptance or the extent to which patients accept the inevitability of chronic pain and engages in activities despite experiencing pain.[188] The recent interest in acceptance and commitment therapy as an effective psychological intervention for chronic pain has precipitated widespread use of the CPAQ.[189] Patients respond to statements of acceptance-related pain beliefs using a seven item Likert scale ranging from one (never true) to six (always true).

The CPAQ has two subscales: engagement in activities and willingness to experience pain.[188] Additional factor analyses have confirmed these two subscales with the scale as published,[190] or with minor revision.[191] Internal consistency coefficients of the total scale range from 0.72 to 0.91.[188,190,192] Regarding validity, the CPAQ has been associated with lower pain severity and pain related disability, less healthcare utilization and medication use, lower self-reported depressive symptoms, pain related anxiety and pain catastrophizing, higher self-efficacy, and lower dysfunctional pain coping and social support interaction styles.[192] The CPAQ has also demonstrated responsiveness to acceptance-based and cognitive behavioral pain treatment,[190,193] as well as a yoga-based pain treatment.[194]

The CPAQ is available in an adolescent version[195] and multiple languages.[196,197] An eight item version of the CPAQ has demonstrated reasonable reliability (internal consistency coefficients = 0.77–0.89) and validity, as evidenced by relationships with pain severity and interference, pain treatment-seeking, and depressive and anxious symptoms.[191]

Quality of Care

The quality of pain care offered to patients can differ substantially by institution, clinician, and individual patient experience. High quality pain care is thought to improve outcomes of pain treatment through a high quality patient-provider relationship and faithful administration of validated treatments.[198] Any effort to improve the quality of pain care across a system must first begin with measurement. For this reason, the American Pain Society produced its first patient outcome questionnaire (APS-POQ) to assess multiple domains of quality of patient care.[199] The most recent version of the measure, the APS-POQ-R,[200] is a 12 item scale that assesses pain severity, the impact of pain on affect, sleep, and activity, side effects, satisfaction with information provided about pain treatment, shared decision making, and use of non-pharmacologic strategies. Patients circles or checks the statement that best applies to their pain management care (e.g. "were you allowed to participate in decisions about your pain treatment as much as you wanted to?" with responses ranging from zero "not at all" to ten "very much so"). In the initial development study, inpatients who had been in the hospital less than 72 h were administered the APS-POQ-R orally, evaluating the first 24 h of their hospital stay.[200] Overall internal consistency was $\alpha = 0.86$. Factor analysis identified five subscales that corresponded with the domains described above, with αs = 0.63-0.83. As with previous versions of the APS-POQ-R,[199] higher pain severity was associated with higher interference with activities, adverse effects from pain treatments, and affective distress, and with lower satisfaction with pain care, providing preliminary evidence for validity.[200] However, cross-cultural validity studies have found poor reliability and inconsistent factor structure in countries other than the United States.[201,202] Findings suggested the APS-POQ-R may be most relevant to patients receiving care within the healthcare system in which it was developed (United States).

In response to concerns about cross-cultural validity, the APS-POQ-R measure was adapted into the international pain outcomes questionnaire (IPO) by PAIN OUT, a multinational European project on postoperative pain management.[203] The measure was developed in two phases, both with large samples (N = 5,134 & N = 4,590) for phases one and two, respectively. Factor analysis found that the final measure loaded on three factors: pain intensity and interference, adverse effects, and perceptions of care. While the IPO questionnaire provides a culturally sensitive alternative to the APS-POQ-R, further validation of the questionnaire across different languages is necessary, as the psychometric validity of the translated versions has not yet been reported.

The pediatric American Pain Society patient outcomes questionnaire (pediatric APS-POQ) was recently developed to assess the six domains—pain intensity, functional interference, emotional response, side effects, perceptions of care, and usual pain—of pain management care in hospitalized pediatric patients.[204] The pediatric APS-POQ was adapted from the APS-POQ-R: wording on items was adjusted for pediatrics, and some items were changed based on updates to the literature. Patient-report and parental-report versions of the pediatric APS-POQ were developed and found to be highly correlated. The measure requires additional testing in more varied populations to establish psychometric validity, as it was developed on a predominately Caucasian, American sample (N = 232) of pediatric patients three years old or older without developmental delays and has not yet been validated in other populations. Additionally, during development, the measure was administered in interview format, and other methods of administration have not yet been validated.[204]

Special Patient Populations

We will briefly review considerations for the psychological and behavioral assessment of pain in the pediatric and older adult populations. Pain is often poorly assessed and managed in these populations, and both require specific considerations and pain assessment measures.[205–208] Further, a substantial proportion of children and older adults cannot self-report their pain, which poses significant limitations to pain assessment.[207]

Recent clinical practice recommendations for pain assessment in patients unable to self-report recommend following a hierarchy of pain assessment techniques: 1) be aware of potential causes of pain; 2) attempt self-report; 3) observe patient behaviors; 4) solicit proxy reporting of pain and behavior/activity changes; 5) attempt analgesic trial.[207] Specific considerations within this hierarchy for pediatric and older adult patients unable to self-report are provided below. As this chapter focuses on the psychological and behavioral assessment of pain, particular attention will be given to these two steps of the hierarchy.

Pain in pediatric patients presenting for health care is extremely common but is generally poorly assessed and treated.[208,209] Clinical practice recommendations suggest considering pediatric patients by cognitive development status. Neonates and infants are unable to self-report as they are nonverbal. However, around the second year of life, children begin to be able to verbalize the presence of pain, and by age three can provide basic descriptions of their pain quality and quantity. Children ages three to six often conflate their affective pain experience with sensory pain symptoms and other aversive physical symptoms and demonstrate reporting bias, making interpretation of self-reported pain scores challenging.[207] The "poker chip tool" (children are asked to pick the number of red poker chips from zero to four that best describe their pain intensity) is recommended for pain assessment in children three to four years old, the faces pain scale-revised is appropriate for children four to 12 years, and the VAS can be used in children eight years and older.[207]

Behavioral pain assessment in pediatric patients can also help identify pain. However, it is important to remember that pain behaviors, and scoring on pain behavior scales, do not necessarily directly correlate with experienced pain intensity. Pain behaviors observed in children differ between acute and chronic pain. In acute pain, facial expressions, physical activity, and crying and other verbalizations are often used as the basis for behavioral pain assessment. In contrast, children experiencing chronic pain tend to limit energy expenditure and display functional limitations. Multiple behavioral pain assessment tools exist for different pediatric populations, including the CHEOPS: Children's Hospital of Eastern Ontario pain scale, CHIPPS: children's and infants' postoperative pain scale, and FLACC: faces, legs, activity, cry, consolability, observational tool (see Herr et al. for further detail).[207] The adolescent pediatric pain tool, based on the MPQ, can provide a useful evaluation of the affective and sensory qualities of pain in children eight years and older. Additionally, the PedsQL provides measures of physical, emotional, social, and academic functioning in children and has both parent and child report versions available. Measures of pediatric pain are discussed further in Chapters 28 and 43.

An estimated 25% to 50% of older adults experience chronic pain. However, multiple barriers to effective pain assessment and management in older adults have been noted, including myths that pain is a normative part of the aging process, stoicism and tendency toward underreporting, fears of opioid addiction, and the increased prevalence of cognitive impairment.[205] Prior to the clinical interview, sensory deficits should be assessed for, and sensory assistive devices should be used as indicated. As with all patients experiencing pain, older adults should receive measures of psychosocial and affective functioning in addition to pain specific self-report assessment measures (see Hadjistavropoulos et al. for a detailed consensus statement on pain assessment in older adults).[205]

Patients with mild to moderate cognitive impairment from dementia can often still self-report their pain, but as dementia progresses, patients' ability to accurately self-report pain decreases.[205] In these cases, observation of patient behaviors—facial expressions, verbalizations/utterances, activity changes, motor movements, and mental status changes—becomes the next best method of pain assessment. The presence of pain indicators should be assessed while patients are in motion, as pain is often less severe at rest.[205] Behavioral pain assessment tools appropriate for older adults with dementia include the CNCPI: checklist of nonverbal pain indicators and the CPAT: certified nursing assistant pain assessment tool.[205] Measures for the assessment of pain in older adults are discussed further in Chapters 44 and 84.

Conclusion

This chapter provides an overview of the role of psychological and behavioral assessment in the context of the provision of comprehensive and integrative care to patients with painful medical conditions. Discussion of more general principles that can be used to guide decisions regarding psychological assessment of pain in the clinical setting was followed by a more detailed consideration of some of the most commonly employed standardized psychological assessment strategies. This review serves as a general guide to clinicians who are compelled by the value of more thorough consideration of psychosocial factors in the assessment of patients with pain that may be used to guide and evaluate pain care. Having acknowledged the potential value of such an approach, several relevant issues that may serve as cautionary notes and targets for future research and clinical investigation may be highlighted.

Of particular note are the overall limitations of this field with regard to consideration of the influence of cultural, racial, ethnic, and other aspects of diverse society on the reliability and validity of existing psychological and behavioral assessment methods. Given a growing awareness and empirical evidence of reliable differences in the experience of pain among patients of differing racial/ethnic backgrounds, gender, and age, among other relevant variables,[210] caution is encouraged when employing most of the reviewed assessment strategies, and specific consideration of culturally specific norms for the measures is important.

Already emphasized throughout this chapter is that several measures frequently used in this field were not originally developed for use with patients with painful conditions, and as a result, the validity of these methods is still subject to concern. The continued development and evaluation of psychological and assessment methods designed specifically for patients with painful conditions and the further evaluation of the psychometric properties of these measures are indicated. With increasing appreciation of differences in the experience of pain and its impact among patients with different conditions, specific examination of the psychometric properties among patients with similar disorders is encouraged. Consistent with this observation, the IMMPACT group, for example, although providing recommendations for the use of specific measures in the assessment of pain treatment effects, has encouraged the selection of measures that were developed and normed for a specific population (e.g. osteoarthritis patients) when such instruments are available.

Another area for continued work is the importance of developing patient-oriented outcome measures. For example, one group

uses a qualitative approach to collect information to develop measures of pain coping in older adults living in the community.[211] Several other investigator groups are currently working on the development and validation of more comprehensive measures for assessing patient-oriented outcomes, and the future availability of these methods promises to provide alternatives to existing methods that may have increased sensitivity to important and meaningful changes in pain and its impact, at least from a patient's perspectives.

Clinicians must consider pragmatic issues related to the use of existing methods and measures for the psychological and behavioral assessment of patients with pain in the clinical setting. Response burden is an important factor to consider when selecting measures for use in the clinical setting. Clinicians are encouraged to consider specific objectives of the assessment and the importance of reaching a balance between the desire for a more thorough assessment and patient burden. Clinicians should also consider measurement precision, brevity, and costs of the assessment process in making decisions about the use of psychological assessment strategies. As already emphasized, the clinical interview and examination remain the core method for clinical assessment and should not be displaced by the use of questionnaires, diaries, and other methods. Finally, managed care reimbursement methodologies are, of course, critical to consider in most clinical settings.

The potential value of incorporating assessment methods that permit a more comprehensive evaluation of the psychological and behavioral aspects of the experience of pain has been emphasized. As in most similar contexts, the "devil is in the details," and clinicians and investigators alike are encouraged to consider a range of important issues when designing an assessment approach consistent with their goals and objectives.

Key Points

- Chronic pain is challenging to assess because pain complaints are inherently subjective, and pain has a wide-ranging influence on patient functioning.
- Psychological and behavioral assessment of pain serves several clinical goals: 1) providing information about a patient's pain experiences, treatment histories, current, and past emotional and physical functioning, and beliefs about pain, 2) identifying the patient's strengths and weaknesses, 3) identifying factors that contribute to the development and maintenance of problems in physical, social, and emotional functioning, 4) identifying comorbid psychiatric or behavioral conditions that may interfere with pain treatment, 5) determining if the patient is psychologically appropriate and likely to benefit from surgery or invasive procedure, and 6) providing a benchmark of the patient's pain and functioning against which the efficacy of treatments can be measured.
- Because of the wide range of clinical goals for psychological and behavioral assessment of pain, when making a request for psychological and behavioral assessment, it is necessary to explicitly state the reasons for the request or pose a question to be answered about the patient or their treatment.
- A useful guide for the assessment of the multidimensional nature of pain is the IMMPACT group consensus statement on the core outcome domains that should be assessed when evaluating the efficacy of a pain treatment and recommended instruments for measuring those domains. The group has encouraged the selection of measures that were developed and normed for a specific population (e.g. low back pain patients) when such instruments are available.
- The consistency, validity, and reliability of the numerous measurement tools have been noted in the following domains: pain intensity, personality, psychosocial impact, physical and social role functioning, emotional functioning, pain beliefs and coping, and quality of care (see Table 22.2). Several of these tools were not originally developed for use with patients with painful conditions, and their validity has not been tested in specific pain populations.
- Technological advances, including smartphone apps and wearable technologies, allow for information about pain, sleep, physical and emotional functioning to be recorded prospectively and frequently in the patients' natural environment. These devices provide objective measures of modifiable health behaviors and are useful tools for clinicians and patients.
- Pain intensity should not be used as a primary, unitary pain outcome measure as it does not directly correlate with pain related disability, and its measurement does not improve the quality of patient pain management.
- Patients with HICP, pain at least most days for ≥3 months with ≥1 activity limitation/participation restriction, experience worse outcomes. Subsequently, providers are encouraged to assess patients for HICP with the question, "Over the past six months, how often did pain limit your life or work activities? Would you say never, some days, most days, or every day?" Patients reporting pain related limitations most days or every day meet the criteria for HICP.
- Pain is often poorly assessed and managed in pediatric and older adult populations, and both require specific considerations and pain assessment measures, particularly for patients unable to self-report pain.
- In patients unable to self-report pain, it is recommended that providers follow a hierarchy of pain assessment techniques: 1) be aware of potential causes of pain; 2) attempt self-report; 3) observe patient behaviors; 4) solicit proxy reporting of pain and behavior/activity changes; 5) attempt analgesic trial.
- Areas for continued research include developing patient-oriented outcome measures, evaluating standard measures in specific populations, and evaluating measures across diverse cultural populations, particularly those with limited communication capability.

Suggested Readings

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23

Disability Assessment

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Introduction

The transition from acute to chronic pain and disability because of multiple factors has been well documented in the literature.[1] According to a morbidity and mortality weekly report from the Centers for Disease Control and Prevention (CDC), one in four United States adults, 61 million Americans, have a disability that impacts major life activities.[2] These numbers are likely to increase in the next few decades with our aging generation of baby boomers currently living with potentially disabling conditions.[3] Continued advancements in medical and surgical technologies enable increased survival after catastrophic injuries and illnesses and may help mitigate the disabling consequences, as well as allow for an increased prevalence of disability within our society. Persons with disabilities face greater barriers to health care than do those without disabilities.[4] Impairment and disability resulting from claims of functional losses secondary to chronic pain continue to challenge pain medicine specialists and independent medical examiners because of the problem's polemic nature. The decade long opioid epidemic has led some in the medical community to question the very existence of disability from chronic pain and the very basis of it as a specific disease entity. Everything about disabling chronic nonmalignant pain engenders controversy except for the suffering associated with the diagnosis and the isolation, frustration, and marginalization experienced by these patients.

Physicians dealing with the evaluation and treatment of patients with chronic nonmalignant pain and disabling conditions can expect to be called upon occasionally to formally evaluate the impairment and disability of these patients for legal purposes, mainly for receiving benefits under many disability compensation systems. This skill is not taught in any medical education or residency training.[5] The treating pain medicine specialist must become familiar with and adapt their practice to better address patient needs associated with these assessment requests by gaining greater knowledge and understanding of the concepts and terminology of disablement and the practices of impairment rating and disability evaluation.

The scientific approach to impairment and disability differs from the legal.[6] To deal with this disparity between law and medicine, a pain medicine specialist must understand the fundamentals of the disability and compensation system, the nuances of legal procedure, and their duties and rights within the legal system. This chapter intends to educate and provide critical information, principles, and practical knowledge unique to the emerging field of disability medicine essential for pain medicine professionals looking to enhance their skills and empower themselves with knowledge, skills, and abilities to further care for their patients. The intention is to not only provide a brief historical and conceptual overview of models of disablement and United States disability systems but also to familiarize the processes and tools available for impairment rating and disability determination and to examine the medical-legal pitfalls and ramifications of these clinical activities. At the conclusion of this chapter, there are also suggestions and recommendations for further reading and available training in disability evaluation.

United States Disability and Personal injuries Compensation Systems

Historical Perspective

It is written in the Bible that "if any would not work, neither should he eat."[7] Hence there has been a long-standing expectation among individuals within society that members must contribute individually to benefit and share collectively. It appears equally valid that individual members who cannot contribute because of disability may be exempt from such expectation and yet still enjoy benefits to which other group members are entitled. It is also possible for an individual to exploit society through unfair and exaggerated claims of disability, which becomes an issue of social justice. Although social justice systems compensate in some way for bodily illness or injury, they must also afford protection against benefits being paid to those who choose not to be productive and fake or exaggerate their disability. Various legal disability and compensation systems provide rules defining disability and entitlement as well as procedures for determining who qualifies as disabled. These rules are intended to provide fair and equitable distribution of limited system resources to those whose needs are greatest and whose disabilities are most compelling.[8]

Within the United States, various disability and compensation systems have arisen to ensure that members of society with a medically determinable impairment that may lead to disability have recourse to compensation from various avenues. This includes state tort laws to provide compensation for personal injuries from intentional or negligent acts of others and state and federal workers' compensation laws for work related injuries and illnesses, social security disability benefits, veterans' benefits, and social

welfare programs where appropriate. These systems have diverse historical origins and statutory requirements. Consequently, there remains considerable variability between them concerning definitions of disability, entitlement, benefits, claims application procedures, adjudication, and the role and relative weight given to medical versus administrative deliberations.

Contemporary Perspective

The United States legal system is complex because of its large territory (50 state jurisdictions plus two commonwealth territories). However, as it relates to disability and compensation of individuals, it is essentially based on two basic types of law: federal and state statutory (legislative) laws and common law (judicial precedent). Both federal and state statutory laws are then mainly adjudicated through administrative law, which has a modified evidentiary and procedural process for ease of judicial administration.[9] The administrative law decisions are then subject to review by various state and federal courts upon appeal by parties. The common law claims of personal injuries, for example, from motor vehicle accidents to slip and fall claims seeking compensation are mainly based on state tort laws.

Tort Law

All states in the United States, under their common law, recognize physical or psychological injury as a personal injury for which monetary damages can be awarded under the law of torts. Common law is a system of law in the United States inherited from the British colonial period based on previous legal judgments (precedent setting cases), which is a defining characteristic of common law sometimes referred to as "judge made law." This is contrasted with statutory law, which is adopted through the legislative process, and regulations enacted by the executive branch. A majority of the United States contract, property, and tort law are based on common law.

Under tort law, a claim is usually made against the defendant for personal injury arising out of negligence and, in some instances, an intentional act. Common examples include those claims arising out of motor vehicle accidents, slip and fall claims against property owners (both private and business), defective products, medical negligence, hospital and nursing home negligence, assault claims, and work related injuries outside of the aegis of workers' compensation. Plaintiffs are entitled to monetary awards for both actual and general damages (e.g. pain and suffering, nonpecuniary damages). The severity of the injury and its outcome in the form of physical or mental impairment and or disability is the main driver for the compensation. Physicians who have not participated in the medical care of the patients are retained by both sides as independent medical examiners (as expert witnesses) to evaluate the plaintiff's claims of personal injury by performing an independent medical examination (IME). The physician is typically required to evaluate the causation, the nature and the severity of the injury, the exacerbation or aggravation of the preexisting pathologic condition, if any, and apportionment. Sometimes, the physician may also be called on to comment on the necessity of the treatment previously provided or future treatment proposed for the condition under question. In addition to the tort claims that may arise from a personal injury caused by motor vehicle accidents, slip and fall, medical malpractice, or defective products are adjudicated in the individual state court system. The following are other contemporary disability compensation systems in the United States.

State Workers' Compensation Systems

The workers' compensation system is statutory law administered by a governing board or agency in each state, commonly referred to as an industrial commission, Bureau of Workers' compensation or commission, which oversees various public/private combinations of workers' compensation systems in that state. In nearly all states, workers' compensation insurance is available through private insurance companies that underwrite the risk of occupational injury/ disease in a particular occupation or industry in return for payment of a premium paid by the employer. A few states have a state-owned monopoly insurance fund that employers must pay into unless they qualify as a self-insurer. Large employers with sufficient financial strength can also self-insure and are responsible for paying the claims through a third party administrator who administers these self-insured workers' compensation programs.[10]

An injured worker is entitled to three types of benefits: medical and rehabilitation expenses, wage loss benefits, and survivor benefits. In the event of death, the surviving spouse and/or children are entitled to survivor benefits. Coverage for medical and rehabilitative expenses is 100% for authorized services. Wage loss benefits are paid according to four separate levels of work disability. Temporary disability occurs for the duration of the treatment period and may be total (employee is incapable of any work) or partial (employee may resume "modified duty" with restrictions).

General damages for pain and suffering and punitive damages for employer negligence are not available in workers' compensation schemes, and negligence is generally not an issue in these cases unless the employer had wanton, reckless disregard to workplace safety, or intentionally caused injury. Thus a workers' compensation system is desirable for employers because the cost of workers' compensation insurance is predictable and can be passed on to the consumer within the cost of goods. In contrast, the employer avoids the potential risk of expensive and time-consuming common law litigation as well as financial insolvency that could result from a substantial jury award.

The workers' compensation statutes in various states may have some subtle differences from each other. However, fundamental features are common to all of these statutory schemes:

- A no-fault system for injuries arising out of and in the course of employment.
- Compulsory insurance is required for employers with very few exceptions.
- Exclusive legal remedy for employees for work related injuries/ illnesses with few exceptions.
- The injured worker retains the right to sue any third party liable for injury.
- Dispute resolution through administrative law adjudication with less rigorous rules of procedure and evidence than the civil court system.
- Expedited benefits for medical and rehabilitation treatment with wage replacement during the temporary disability phase.
- Final compensation for permanent partial and permanent total disability.

Under the workers' compensation system, upon completion of the treatment phase under a claim, a physician must determine the point of maximum medical improvement (MMI) so case closure can occur. The employee may receive monetary compensation for permanent total or partial disability. Generally, this is a lump sum payout calculated according to a predetermined formula specific to each jurisdiction. It considers the value of the "whole person impairment" as several weeks' pay multiplied by the average

weekly wage up to a cap, and then multiplies by the impairment percentage of the "whole person" based almost always on a certain edition of *American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment* as prescribed by the relevant law or regulation.

Medical determination of physical or psychological impairment is almost always performed at MMI by a physician skilled in the use of the *AMA Guides,* as impairment is only determinable by medical means. In contrast, disability requires consideration of numerous other non-medical factors. However, in some cases, the physician is empowered to render an opinion regarding the nature and extent of medically determined impairment resulting in disability.

Federal Workers' Compensation Systems

In the United States, federal workers' compensation laws provide no fault based compulsory broad coverage of injuries and illnesses arising out of and in the course of employment for over 2.9 million federal employees. The United States Department of Labor (USDOL) maintains exclusive jurisdiction over these programs subject to judicial review.

The major federal workers' compensation programs are administered by the Office of Workers' Compensation Programs (OWCP), an agency within the USDOL. One of the major federal programs, the Federal Employee's Compensation Act (FECA), covers federal employees in more than 70 different agencies along with several other worker groups adopted by Congress in various acts of expansion of the federal authority.[11] Additionally, the Longshore and Harbor Workers' Compensation Act, Energy Employees Occupational Illness Compensation Act, and Federal Black Lung Program (coal mine workers' compensation) are other federally mandated compensation acts administered by the OWCP. These four major federal workers' compensation programs provide wage replacement benefits, medical treatment, vocational rehabilitation, and other benefits to injured workers that experience work related injury or occupational disease or their dependents.[12] USDOL also oversees the Defense Based Act (DBA) that provides workers' compensation protection to civilian employees working outside the United States on military bases or under a contract with the United States government for public works or national defense. Similar programs that cover a specialized group of workers, such as the Non-Appropriated Fund Instrumentalities Act (NAFIA) and Outer Continental Shelf Lands Act (OCSLA), exist but are beyond the scope of this discussion.

Other federally mandated workers' compensation programs include the Federal Employers Liability Act (FELA), commonly known as the Railroad Worker Act, and the Jones Act (Merchant Marine Act). FELA provides disability benefits to employees of the interstate railroad industry for job-related injuries. It is the only remedy for injured railroad workers employed by a common carrier railroad. It is a fault-based system, and the injured railroad worker must sue the railroad in civil court (similar to negligent tort action) to prove that the injury was caused in whole or in part by the negligence of an agent, employee, or contractor of the railroad or from faulty equipment. The civil action can be brought in either a state or federal court, and the case is tried in front of a judge and jury. The monetary damages awarded against the negligent railroad are generally much higher than those of other no fault based state or workers' compensation systems.[13]

The Merchant Marine Act of 1920, also known as the Jones Act, allows civilian sailors, while in the service of a ship in the United States navigable waters and between United States ports, to claim compensation for injuries resulting from the unseaworthiness of the vessel on which they served or negligence of a ship's owner, agents, and employees. It operates similar to FELA, and the claimant must bring suit in civil court against the master or owner of the ship to collect monetary compensation.

Social Security Disability Benefits Program

The Social Security Administration (SSA) manages the largest federally mandated disability insurance program in the United States, providing benefits to approximately half of all persons who qualify as disabled under its two titles. Social Security Disability Income (SSDI; Title 2) covers individuals who are disabled (unable to engage in substantial gainful activity) because of a medically determinable physical or mental impairment that has lasted or is likely to last for more than 12 months or is likely to result in death.[14] It is currently funded by a payroll tax contributed to by both the employer and, while gainfully employed, the employee. Self-employed workers are also required to contribute to the system. Benefits are available to those individuals who have worked in a qualified job for a requisite period, paid into the social security system, and subsequently become disabled before age 65 years. SSDI benefits are provided to those considered totally incapacitated and extend to their surviving spouse and children. Benefits are paid as a monthly stipend, and beneficiaries may receive payments until age 65 years, after which they are eligible for social security retirement benefits.

Supplemental Security Income (SSI; Title 16) is a second disability benefits program within the SSA, which operates as a federal-state partnership providing SSI benefits to disabled individuals whose income and assets meet minimum criteria according to a means test. It is funded through general revenue (i.e. income tax revenues) and does not require work history for eligibility. Most SSI recipients are below the federal poverty income threshold and must remain below that threshold to continue receiving SSI, but this is not the case with SSDI.[15] The SSI provides income for medically indigent persons who are blind, disabled, or older (>65 years of age). SSI also provides assistance to children if they have "medically determinable impairments of comparable severity" to an adult's and if the impairment "limits the child's ability to function independently, appropriately, and effectively in an age-appropriate manner."[16] SSI operates as a federal-state partnership and, in addition to the means test, also requires that a "medically determinable impairment" be established.

When an applicant submits an SSI application, and non-medical eligibility has been established, the application is forwarded to their state Disability Determination Service (DDS) for further medical review. The SSI has its own set of medical criteria, the "listing of impairments," which, if met or equaled, will cause an automatic award of benefits. There are separate listings for adults and children arranged by body system. Each listing typically contains a diagnosis and some clinical markers of severity. If listing criteria are not met, the applicant can appeal based on "residual functional capacity."

Physicians, including the patient's treating physician, who assist applicants when filing for SSDI or SSI disability, should be familiar with the "five-step" appeals process and the listings themselves.[17] They may be asked to provide the DDS evaluating team with a statement about the patient's ability to do work related activities and backed by objective evidence. They may also be asked to comment on an applicant's physical and psychological capacities and limitations. If the condition in question does not

meet or equal the listings, to assist the DDS evaluating team in estimating the claimant's "residual functional capacities."

Disability Benefits Under the Veterans Benefits Laws

The Veterans Benefits Administration (VBA) within the Veterans Health Administration (VHA) oversees the Department of Veterans Affairs' (VA) compensation and pension program (C&P) providing service to United States veterans.[18] Eligibility for VA disability benefits is based on discharge from active military service (full-time service to the army, navy, air force, marines, or coast guard, or as a commissioned officer of the Public Health Service, the Environmental Services Administration, or the National Oceanic and Atmospheric Administration). Only honorable and general discharges (as opposed to dishonorable or bad-conduct discharges) qualify. Entitlement to compensation is determined by the Adjudication Division of the C&P Service within the VBA. It is classified as service connected if the disability relates directly to injury or disease incurred while on active duty or as a direct result of VA care or as nonservice connected if determined to have not been incurred while on active duty. Presumptive service connection applies to various conditions, such as chronic diseases (e.g. hypertension, diabetes mellitus) or tropical diseases (e.g. malaria), and qualifies for compensation if such conditions manifest themselves within one year of discharge from active duty.

Disability compensation is paid as a monthly stipend to veterans who are disabled because of service connected injury or disease. The amount of compensation received depends on the amount of impairment caused by the injury or disease where the rating percentages themselves are expressed according to "the average impairment in earning capacity resulting from such disease and injuries and their residual conditions in civil occupations." Disability compensation is not subject to federal or state income tax, it varies according to the number of dependents, and it is regularly adjusted to reflect changes in the cost of living. Benefits may also include disability pensions for veterans of low income according to a means test, who are permanently and totally disabled, and who have experienced 90 days or more of active duty, at least one day of which was during wartime. Other benefits include insurance benefits, specially adapted housing, motor vehicle modifications, and durable medical equipment.

The benefit amount is based on the VA Schedule of Rating Disabilities (VASRD), a graduated scale from 10% to 100% (in increments of 10%) depending on the degree of the veteran's disability based on medical evidence. The multiple percentages are combined using a combined rating chart similar to the combined values chart in the *AMA Guides to Evaluation of Permanent Impairment.*[19]

VA C&P examinations may be performed by physicians, nurse practitioners, physician assistants, psychologists, optometrists, audiologists, and "other qualified" clinical personnel. The VHA oversees and ensures that C&P examiners are adequately qualified, and all C&P examination reports must be assigned by a physician or psychologist. The physician examiner is asked to render an opinion as to the diagnosis of the ratable condition, to address permanency of the condition, and to opine as to whether the individual with the condition is considered totally disabled (fails to meet minimal employability criteria), which is defined as physical inability to be employable at a sedentary level, or psychiatric or psychological inability to be employed in a loosely supervised situation with minimal exposure to the public.

Physician disability evaluations are generally performed at VHA facilities with the automated medical information exchange data processing system and associated disability examination worksheets disability based questionnaires (DBQ) and the VA's schedule of rating disabilities.[20]

The adjudication division of the C&P programs, through its rating officers (rater), determines the nature and amount of entitlement benefits, which include monthly disability payments to the veteran or the veteran's spouse, child, or parent in the event of a service connected death. Additional benefits include hospitalization and medical care, orthotic and prosthetic devices, durable medical equipment, and allowances for adaptive modifications to the veteran's home and/or motor vehicle where necessary. Title 38 of the Code of Federal Regulations contains both the VA's schedule for rating disabilities in Part 4 and other VA regulations about compensation and pension in Part 3. The schedule is organized according to 16 body parts and systems.

Private Disability Benefit Systems

According to some estimates,[21] about 40 million Americans are covered by private short and long term disability insurance that pays replacement income in the event of a temporary or permanent disability that prevents the insured from working. Private disability insurance generally available through the workplace is a contract between the insurer and insured. Specific contractual language governs the criteria for eligibility, entitlement, and benefits. The injured party must complete a certain waiting period (usually three months), after which the long term disability policy takes effect. Such policies may be group policies (more affordable) with coverage to individuals who cannot perform their usual and customary job during a finite period (typically two to three years). Subsequently, disability benefits may continue only if the individual can be determined unable to perform any occupation according to the definitions and provisions of their policy. Private disability generally pays up to 60% of the individual's wages (to a cap) and may have a built-in cost of living allowance to adjust for inflation.

Working Terminology and Definitions

Physicians performing impairment and disability evaluations must be familiar with precise meanings and definitions of the terms impairment and disability, as well as the fundamental requirements, nuances, and jurisdictional variations of the particular disability system within which they are working. See Table 23.1 for a comparison between various disability compensation systems in the United States and a section on working terminology and definitions.

To effectively communicate medical and other scientific information to claims examiners, claims managers, lawyers, and adjudicators, doctors must become familiar with the important definitions and terminology that are commonly used in disability assessment and medicolegal practice, as some are "terms of art" having specific meanings within the field of disability medicine that differ from their traditional meanings.[22] This section defines common medicolegal terms that physicians dealing with disability evaluation should be familiar with and includes annotations for better understanding.

TABLE 23.1 Comparison of Major Disability Compensation Systems in United States

Compensation System	Eligible Individuals	Adjudicating Body	Rating Schedule	Employability Status	Benefits	Maximum Monthly Benefit
State tort laws	Personal injuries resulting from negligence or intentional acts of others	State court system by civil actions (lawsuits)	Jury award for both compensatory and general damages, i.e. pain and suffering	Based on state tort law	Damages for various pecuniary and non-pecuniary losses	Lump sum award
State workers' compensation	Workers injured out of and in the course of employment in a particular state. Excludes federal employees	Individual state worker's comp statutes	AMA *Guides* in most states; particular edition of *Guides* prescribed by law. Few states have their own rating guide	Return to work in one's own occupation, or in modified duty, if available	Medical and rehabilitation benefits, wage loss benefits. Survivor's benefits. Permanent partial or total disability benefits	Determined by statute
Social security	Workers <65 years or survivors who are or have contributed to the SS Trust Fund (SSDI); needy disabled children, aged, disabled and blind adult (SSI) without means for support	Social security administration	*Disability evaluation under social security schedule. (listing of impairments)*	Unable to engage in the substantial gainful activity by a physical or mental impairment for >12 months	Monthly stipend	There is an annually adjusted cap on benefits
Federal employees' compensation act (FECA)	Federal employees, including the United States postal service, peace corps	United States department of labor (USDOL)–office of workers' compensation prog. (OWCP)	AMA *Guides sixth edition*	Loss of earnings (no schedule loss) because of disability resulting from personal injury sustained while in the performance of duty	66.6%–75% of wages, reasonable medical care. Lump sums not available	75% of wages if worker married or has dependents
Longshore and harbor workers' compensation program	Maritime employees such as seamen, longshoremen, harbor workers, ship workers (not seamen)	Office of workers' compensation programs in the United States department of labor	AMA *Guides* 6th *edition*	Wage loss and schedule loss benefits for injuries arising out of and in the course of employment	Full medical care, death benefits, lump sum awards, 66.6% of weekly wages	200% of the current national average weekly wage
FELA-railroad workers' act and Jones Act for seamen	Railroad workers and seamen	Federal or state court system by civil actions (lawsuits)	Jury award for both compensatory and general damages, i.e. pain and suffering	Based on FELA or Jones Act as the case may be	Damages for various pecuniary and non-pecuniary losses	Lump sum award

Continued

TABLE 23.1 Comparison of Major Disability Compensation Systems in United States—cont'd

Compensation System	Eligible Individuals	Adjudicating Body	Rating Schedule	Employability Status	Benefits	Maximum Monthly Benefit
Veterans disability programs	Honorable or general discharge from the armed forces or a survivor of a veteran	Adjudication division of the compensation and pension service of the veterans benefits administration	*VA schedule for rating disabilities (VASRD)(Ref)*	Wage loss and schedule loss for the average person unable to follow a substantially gainful occupation	Disability pension, death benefits, hospitalization, medical care, orthotics, prosthetics, durable medical goods, adaptive modifications	Variable based on rating and other criteria
Private disability insurance	Individual covered under a long term disability insurance plan after a wait period of short term disability defined by the policy	Long term private disability insurance company	Based on the contractual language of the disability insurance policy	Inability to engage in own occupation up to 3 years, or in any occupation, after that, depending on the individual policy	Wage loss compensation	Generally, 60% of previous income

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Key Terminology and Definition

Abnormal illness behavior: Conscious or unconscious, intentional or unintentional exaggeration or fabrication of symptoms and/or physical findings because of psychological, social, financial, or other reasons.

Accommodation: In the context of the Americans with Disabilities Act, any modification of the workplace or a specific job that allows a person with a disability to perform essential functions of a job and/or able to be gainfully employed.

Activities of Daily Living (ADLs): Basic self-care activities performed in one's personal sphere (e.g. feeding, bathing, hygiene, dressing). Instrumental ADLs (IADLs) are complex self-care activities that may be delegated to others (e.g. financial management, medications, meal preparation). ADLs do not include highly individualized work duties.

Adjudicate: To make a formal judgment on a disputed matter through judicial authority.

Administrative hearing: An oral proceeding similar to a trial with the presentation of testimony and evidence before an administrative hearing officer or a law judge. Unlike a trial, an administrative hearing is usually less formal and shorter in duration with abbreviated procedural rules.

Administrative law: The body of law that governs all the activities of administrative agencies of government, including rule making, adjudication, or the enforcement of specific regulatory mandates given by the legislative bodies.

Affidavit: A written statement under oath for use as evidence in a legal proceeding subject to the penalty of perjury for falsehood as if giving false evidence in court.

Aggravation: Permanent worsening of a preexisting condition.

Allegation: A claim or assertion of a fact by a party in a legal proceeding made without proof.

Apportion/Apportionment: To divide something proportionally, such as allocating contributions among various causes of disease or impairment. The first step in causation apportionment is scientifically-based causation analysis.[23] Second, one must allocate responsibility among the probable causes and select apportionment percentages consistent with the medical literature and facts of the case in question. Arbitrary, unscientific apportionment estimates, which are nothing more than speculations, must be avoided.

Case law: Accumulated decisions and holdings by appellate courts interpreting and applying legal principles, common law, statutes, or provisions of a constitution in previous cases. The aggregate of reported cases sets the precedents (authority) that must be followed as the law (binding) by the lower courts within the same jurisdiction when deciding subsequent cases with similar issues or facts in similar cases. The legal principle *stare decisis* (Latin for "to stand by the things decided") requires that similar cases be treated alike to create stability and predictability in common law.

Cause/Causation: In general, anything that produces an effect. In medicine, cause refers to an identifiable factor (e.g. trauma, toxic, or infectious exposure) that results in injury or illness. The cause or causes must be scientifically probable following causation analysis.

Cause of action: Legal grounds for which a plaintiff can sue in court for the legal wrong the defendant is alleged to have caused. A specific legal theory upon which a plaintiff can legally sue and seek legal remedy. Some examples are medical malpractice, intentional infliction of emotional distress, battery, false imprisonment, or breach of contract.

Civil action: A legal proceeding (lawsuit) by a party to enforce, redress or protect private rights and mostly seek relief in the form of the monetary damage award. These suits most often

are between private parties, although governments and corporations may be parties to a civil lawsuit.

Claim adjuster: Usually an insurance company employee or an independent agent who investigates insurance claims to determine the extent of the insuring company's liability, assesses the amount of compensation to be paid and negotiates and settles claims against the insured.

Combined Values Chart: A method used in the *AMA's Guides to the Evaluation of Permanent Impairment (AMA Guides)* to combine two or more impairment percentages, derived from the formula A + B (1 – A) = Combined Values of A and B. Combining, as opposed to adding, ensures that the total value will not exceed 100% whole person impairment and considers the impact of impairment from one body part on impairment of another body part.

Compensable injury: Workers' Compensation statutes define this as an injury or illness arising out of and in the course of employment.

Contingency fee: A charge or fee, the collection of which is based upon the client winning or settling the case.

Contract: A legally binding and enforceable agreement made between parties.

Cross examination: The interrogation under oath to test the truthfulness of witness testimony in a legal proceeding (deposition or trial) by challenging or probing the testimony given during the *direct examination* that precedes the cross examination.

Damages: In law, damages are monetary sums awarded by a court in a civil action as compensation to someone who has been injured or suffered loss because of the wrongful conduct of another party. In a tort action, damages are meant to restore an injured party to the position before being harmed, which in addition to being compensatory (reimbursement for actual losses such as lost income and medical expenses), also include general damages that are non-economic (non-pecuniary) losses, such as pain and suffering, mental anguish, loss of life's enjoyment, loss of consortium, and so on.

Deposition: A process of taking testimony under oath of a witness (deponent) by oral interrogations outside the trial by an attorney for the parties involved in civil litigation. Usually, depositions for a physician witness are done as pre-trial fact findings in which the retaining counsel asks questions (direct examination), and the other side then tests the truth of the witness statements by cross examination. The questions are asked by attorneys in the same manner as if the witness was testifying in a live trial. The proceeding is recorded by a court reporter, and a transcript of the testimony is produced that may be submitted as evidence or used to impeach the witness at trial by confronting the witness with inconsistencies in statements.

Direct examination: The primary or initial questioning (also known as examination in chief) of a witness by the party that has called that witness to give evidence that supports their case.

Disability: An umbrella term for activity limitations and/or participation restrictions in an individual with a health condition, disorder, or disease. The definition may differ and be more specific in certain compensation systems. For example, the United States SSA defines disability as the inability to engage in substantial gainful activity because of a medically determinable physical or mental impairment that has lasted for 12 months or likely to result in death.

Exacerbation: Temporary worsening of a preexisting condition. Following a transient increase in symptoms, signs, disability, and/or impairment, the person recovers to her baseline status, or what it would have been had the exacerbation never occurred.

Expert witness: A person tendered as a witness in a legal proceeding stipulated as having special knowledge, education, training, experience, or skill in a field for which she may give testimony if it assists the trier of fact (jury or the judge) in determining the truth of a matter.

Impairment: A significant deviation, loss, or loss of use of any body structure or function in an individual with a health condition, disorder, or disease.

Impairment evaluation: The acquisition, recording, assessment, and reporting of medical evidence, performed by a licensed physician, using a standard method such as described in the *AMA's Guides to the Evaluation of Permanent Impairment (AMA Guides)*, to determine permanent impairment associated with a physical or mental condition.

Malingering: According to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*, malingering is not a psychiatric condition but rather a conscious and intentional production of false or grossly exaggerated physical or psychological problems motivated by external incentives such as avoiding military duty or work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs.

MMI: Also known as the maximum degree of medical improvement, it is the point at which a condition has stabilized and is unlikely to change (improve or worsen) substantially in the next year, with or without treatment. While symptoms and signs of the condition may wax and wane over time, further overall recovery or deterioration is not anticipated. Simply put, the person is now as good as they are going to get, signifying that the injured person can exit the temporary disablement stage of recovery, facilitating claim settlement and case closure.

MMI does not preclude the deterioration of a condition that is expected to occur over time, i.e. beyond 12 months; neither does it preclude allowances for ongoing follow-up or maintenance medical care, should such care be indicated based on current evidence-based practice generally accepted by the scientific community.

However, both the name given to and exact definition of this status vary depending on the jurisdiction. Among the numerous synonyms for MMI are (in alphabetical order): ascertainable loss, end of healing, fixed and stable, maximum cure, the maximum degree of medical improvement, maximum medical healing, maximum medical recovery, maximum medical rehabilitation, maximum medical stability, medical end result, medical stability, medical stabilization, medically stable, medically stationary, permanent and stationary, and stable and ratable.

Negligence: Failing to exercise the degree of care that a reasonably prudent person would exercise under the same or similar circumstances. It can also be thought of as a breach of legal duty that causes an injury resulting in liability to the injured party.

Pecuniary: Pertaining to money as in pecuniary damages awarded for actual monetary losses.

Permanent impairment: The impairment present at the point of MMI.

Reasonable degree of medical certainty/probability: Two phrases commonly used in medicolegal reports and expert testimony to express the idea that their opinions are based on at least a 51% probability conveying that the opinions are "more probable than not" correct or true.

Rules of civil procedure: A body of law that provides the rules that courts must follow when adjudicating civil lawsuits.

Stare decisis: Latin for "to stand by the things decided" or also "let the decision stand." A legal principle requiring courts to apply the same approach and rationale of the legal principles

as decided in similar prior cases setting precedent. See also *case law*.

Statute: A written law enacted by a legislative body (state or federal) that declares, forbids, or commands something specific to achieve a specified legislative objective.

Subjective: In health care, refers to that which is perceived, reported, and/or demonstrated by a patient but cannot be verified by an examiner on physical examination or via diagnostic tests. The adjective is most commonly used in the context of symptoms such as pain, but many physical findings are also subjective, including tenderness, range of motion, and strength.

Subpoena: An official written command issued in judicial process directing the person to appear at a certain time and place to give testimony under oath or provide documents in her possession or control (*subpoena duces tecum*) that may help resolve an issue in a pending litigation.

Whole person impairment: A concept described in *AMA Guides* that relates the impact of the impairments from various body parts on the individual's overall ability to perform ADLs, excluding work.

Models and Classification of Disablement

Models of Disability

The "medical model" of disability was the paradigm for understanding disablement throughout much of the 19th and 20th centuries, during which causation of disability was directly viewed in terms of the underlying pathology (impairment) arising through illness or disease. Management of disability was closely linked to the diagnosis and treatment of the underlying pathology, long considered the purview of the physician examiner, who then became empowered to rate and diagnose and treat the disabling condition (impairment). Anatomic and physiologic objectivity is the conceptual lynchpin of the medical model of disability described above.[24] This model worked well for conditions whereby the diagnosis was unambiguous, and the pathology was well understood, and where treatment strategies and end points were often well established and clearly understood.[25] Today, the medical model still serves as the basis for social security disability determinations as described in some of the compensation systems in section III above.

The "social model" of disability grew out of the disability advocacy movement of the 1970s and 1980s and was founded on the notion that society imposes disability upon individuals with impairments by failing to address their special needs in terms of priority awareness, environmental access, and infrastructural accommodation for major life activities. The resulting disability was viewed in terms of restrictions imposed upon the impaired individual ranging from individual and institutional prejudicial thinking and discrimination, architectural and other physical barriers to access and transportation, educational segregation, and the lack of accommodation in the workplace.[26]

An understanding of the social model has helped foster strategies to better neutralize social barriers to individuals with impairments, enabling them and minimizing their disability.

The "biopsychosocial model" of disability[27] is now widely accepted as the preferred conceptual model of disablement. It simultaneously recognizes the contributions of medical, social, personal, and psychological determinants of disability. The *biologic* component refers to the physical and/or mental aspects of an individual's health condition. The *psychological* component recognizes personal and psychological factors that are impacting that individual's functioning. The *social* component recognizes contextual and environmental factors that may also affect functioning in each case.[28]

Classifications of Disablement

The most commonly used, contemporary, internationally-accepted definitions, terminologies, and classification of disablement have been created by the World Health Organization, the origins of which can be traced to the work of Bertillon's *Classification of Causes of Death* (1893), which later was expanded into the *International Statistical Classification of Diseases, Injuries and Causes of Death*.[29] In 1948 the World Health Organization took over this effort, which ultimately led to creating the *International Classification of Impairments, Disabilities and Handicaps* (ICIDH) in 1980.[30] This system applied a model of disablement with four ordinal domains linked in a linear relationship as follows (Fig. 23.1).

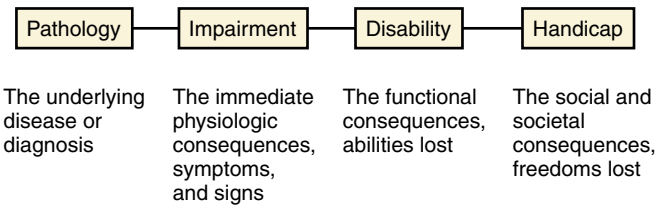
Pathology - "a disease or trauma acting at a tissue anatomical or physiological level to potentially alter the structure and/or function of an organ."

Impairment - "any loss or abnormality of psychological, physiological or anatomical structure or function and resulting from a pathology." Impairment occurs at an organ system level.

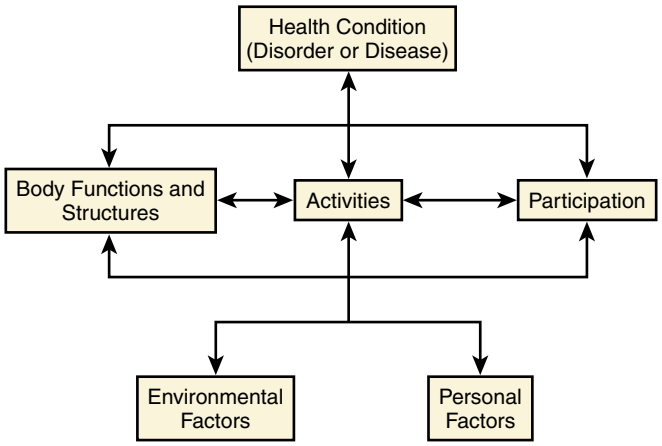
Disability - "any restriction or lack (resulting from impairment) of ability to perform an activity in the manner or within the range considered normal for a human being." Disability is commonly conceptualized in terms of limitations on activities within one's sphere, including mobility (transfers and ambulation) and self-care (activities of daily living or ADLs).

Handicap - "a disadvantage for an individual that limits or prevents the fulfillment of a role that is normal (depending upon age, sex, social and cultural factors) for that individual."

There were several shortcomings of the ICIDH system. It was rooted in the medical model of disease whose limitations are described above. The linearity of the system implies a unidirectional and causal relationship among its elements which may not always be the case. It inadequately accounted for various modifiers (e.g. personal, environmental), which could influence the magnitude of disability.[31] For example, other work showed that environmental factors played a key role in determining outcomes of disability that could be studied independently.[32] Subsequent work by the Institute of Medicine (IOM)[33] and the National Center for Medical Rehabilitation Research,[34] expanded upon the view that resulting disability was the product of the individual with an impairment interacting with their environment in each specific case. Additional attention was given to the role of personal modifiers (e.g. lifestyle choices, belief systems, entitlement, and coping abilities) affecting outcomes of disability for individual cases.[35]



• **Figure 23.1** World Health Organization's international classification of illness. (Reproduced with permission from World Health Organization. *International Classification of Impairments, Disabilities and Handicaps*: *A Manual of Classification Relating to the Consequences of Disease*. Geneva, Switzerland: World Health Organization; 1980. Figure 2*.)



• **Figure 23.2** Components and interactions of the World Health Organization's international classificaion of funtioning. (Reproduced with permission from World Health Organization. *International Classification of Functioning, Disabilities and Health: ICF.* Geneva, Switzerland: World Health Organization; 2001.)

The International Classification of Functioning, Disabilities, and Health (ICF)[36] is depicted in Fig. 23.2.

The ICF has replaced the ICIDH and portrays an interactive (as opposed to linear) association between an individual with a health condition, the functional consequences of their impairment, and contextual factors of a personal and environmental nature. The ICF classification system embraces the biopsychosocial model of disease described earlier, considering environmental and personal modifiers of functional outcomes in any given case.

The components of disablement according to the ICF classification system include:

Body functions and body structures: physiologic functions and body parts, respectively.

Activity: the execution of a task or action by an individual (typically within their personal sphere).

Participation: involvement in a life situation (typically within a social sphere).

Impairments: problems in body function or structure such as a significant deviation or loss.

Activity limitations: difficulties an individual may have in executing activities.

Participation restrictions: problems an individual may experience in involvement in life situations.

Within this conceptual framework, the disabling consequences of impairment may be amplified or mitigated by factors unique to the individual with a health condition, interacting with their environment and according to personal choice. To illustrate the importance of environmental factors, consider Fig. 23.3.

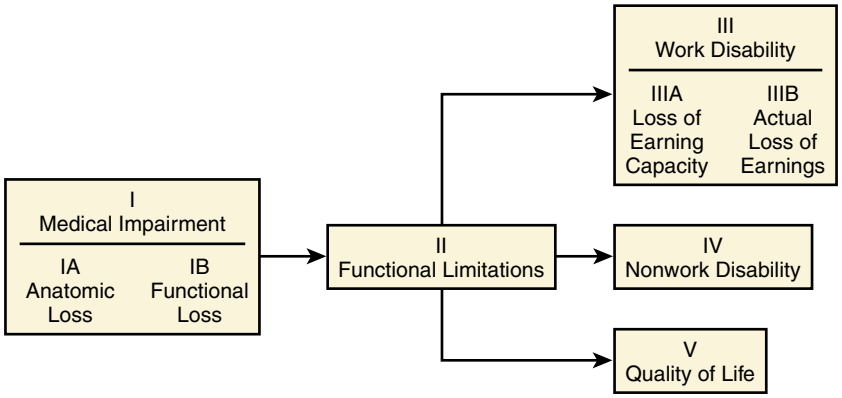
Despite its superiority as a classification system, shortcomings of the ICF can be noted. The distinctions between activities and participations are often blurred, and inadequate attention has thus far been given to quality of life (QOL) measures (e.g. life satisfaction, burden of care) in the model itself.

Measuring Disability for Compensation Purposes

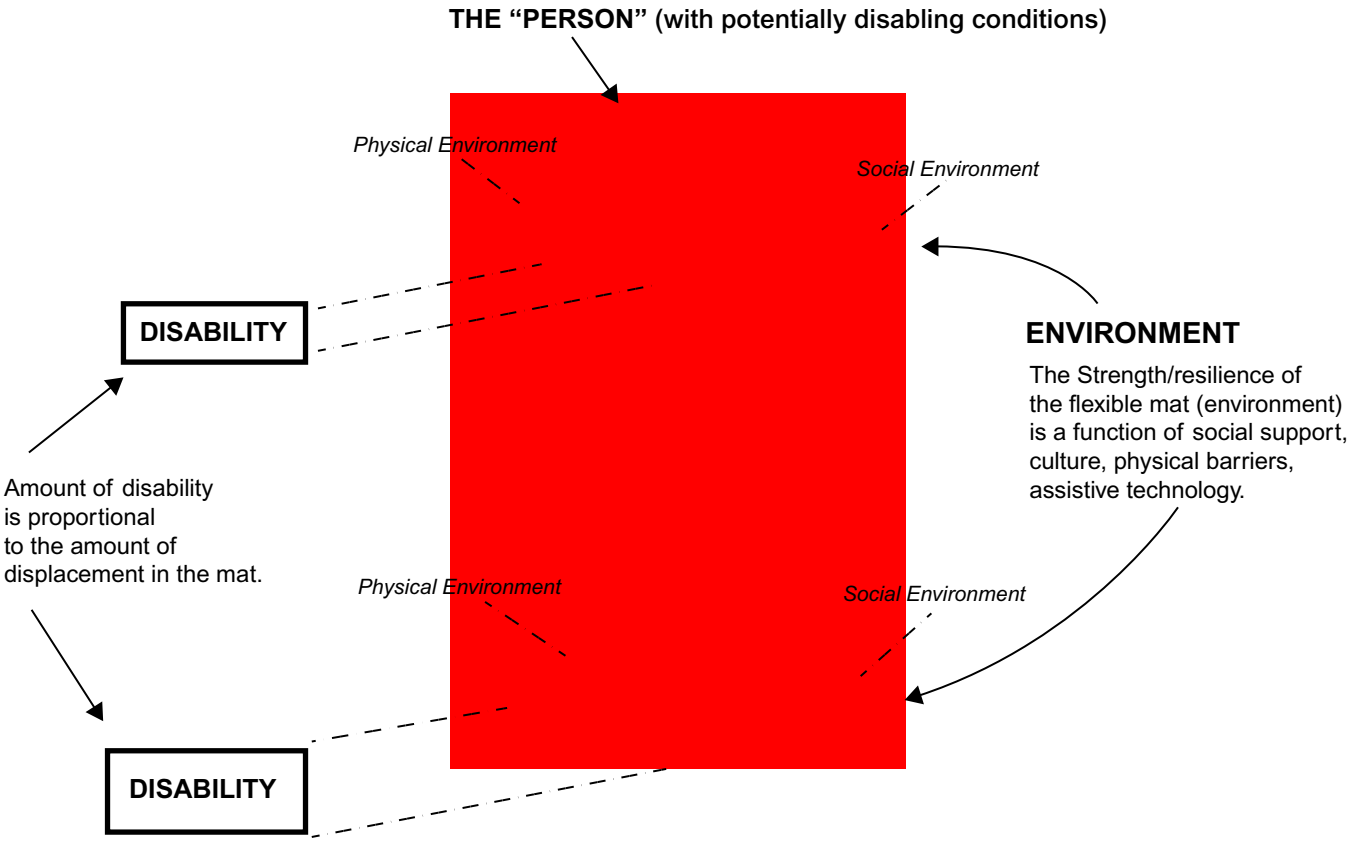
Social justice requires that individual group members contribute productively to the common good of the whole. However, provisions must be made to exempt this requirement and support those incapable of such productivity by virtue of age, illness, or disability. A related expectation is that individuals who incur loss or disablement because of illness or injury are thereby entitled to some compensation for their losses.

Within our social system, there are many different disability compensation systems (see section III above) designed to compensate individuals for such losses. They share a common conceptual and operational platform in which the initial estimate of physical and/or psychological loss can be translated into an estimate of functional and economic losses expressed in monetary terms.

By convention, the severity of the physical and psychological loss is operationally defined and measured in terms of a *medical impairment rating* at an organ system level. That is typically expressed as a percentage of regional loss of the affected body part(s) and can be further extrapolated to the body as a whole. The severity of functional and, hence, economic loss associated with this impairment percentage is further estimated in terms of a *disability rating* expressed as a percentage of the economic worth of the "whole person." The disability rating is operationally derived from the impairment percentage and is at once intended to reflect direct economic losses, non-economic losses, and negative impact on QOL in terms of a monetary sum. The whole person value and magnitude of awards vary according to the disability system in question, and disability payments may be awarded as lump sum payments or on an annuity basis.



• **Figure 23.3** Disabling consequences of an injury or disease. (Reproduced with permission from McGeary M, Ford M, McCutchen SR, et al. (eds). *IOM Committee on Medical Evaluation of Veterans for Disability Compensation. A 21st Century System for Evaluating Veterans for Disability Benefits. The Rating Schedule*. Washington, DC: The National Academies Press; 2007, pp. 117.)



• **Figure 23.4** Reproduced with permission from the Institute of Medicine. *Enabling America: Assessing the Role of Rehabilitation Science and Engineering*. Washington, DC: The National Academies Press, 1997. doi:10.17226/5799.

The IOM[37] has recently developed a generalized model to demonstrate the essential features common to all disability systems. Individuals seeking compensation and meeting criteria of entitlement must demonstrate losses according to five domains of interest (see Fig. 23.4).

The first of these, *Medical Impairment*, traditionally carries the most weight for several reasons. It is largely anatomically and physiologically based and, hence, can readily be measured in objective terms. Objectivity enables codification of the disability and fosters standardization, reliability, and reproducibility of measurement according to some uniform scale. Impairment can be measured and expressed in terms of anatomic or functional losses.

The second domain of interest, *functional limitations*, can be expressed and measured in terms of basic ADLs and/or instrumental (advanced) activities of daily living (IADLs). ADLs include basic self-care activities such as feeding, toileting, grooming, bathing, hygiene, and dressing—activities that generally occupy our personal sphere. IADLs require greater cognitive and physical capacity and include such activities as meal preparation, driving, managing finances, medications, and one's daily routine.

The third domain, *Work Disability*, can be understood in terms of loss of earning capacity (an actuarial determination of negative impact on employability and earnings brought about by work restrictions because of the impairment, and other considerations such as age, baseline employment, and earnings history, availability of accommodation and alternative job opportunities, and other local factors). It can also be understood in terms of actual loss of earnings directly attributable to the impairment.

A fourth domain, *non-work disability*, includes losses in terms of inability to visit friends and relatives, engage in communal activities, hobbies, or other recreational pursuits because of barriers of access or performance attributable to the impairment.

A fifth domain, *QOL*, includes losses attributable to diminished life satisfaction, self-esteem, and increased burden of care in terms of treatment compliance and caregiver support.

The metrics whereby each of these constructs is defined and measured vary and remain incompletely understood. This is partly because of persisting confusion of terminology, definitions, and criteria of impairment and disability across the various systems and the continuing emphasis upon objective, medically determined impairment as the prime determinant of disablement.

Unfortunately, there is also a lack of agreement upon the metrics whereby the impairment ratings themselves are determined between and even within the various disability systems of interest. For example, United States workers' compensation jurisdictions show considerable variability in terms of their acceptance or rejection of standard and uniform impairment rating guides and those that mandate or recommend the use of the same variable in the choice of reference. Even in the case of the *American Medical Association Guides to the Evaluation of Permanent Impairment (AMA Guides)*, the actual edition chosen for reference varies from state to state.[38] The same is true for the international use of the *AMA Guides* where in many countries (e.g. Australia, Netherlands, South Africa), the various editions are used in motor vehicle accidents and other personal injury claims to determine the injury severity (a threshold) before access to benefits for general damages (non-pecuniary, non-economic losses) is granted.[39]

The importance of the impairment rating to cash awards also varies within and between the various disability systems, as a closer examination of the United States workers' compensation (WC) system illustrates. Operationally, the WC system awards cash benefits according to three basic approaches: The first of these, the *impairment approach*, awards benefits in direct relationship to the percentage of impairment rating. The second, the *loss of earning capacity approach,* requires that the injured worker have an impairment rating but then bases the actual amount of cash benefits on the estimate of associated loss of earning capacity. The third approach, the *actual wage loss approach*, requires the worker to have both an impairment and loss of earning capacity and then base the amount of cash benefits on demonstrating the actual loss of workers' earnings.[40]

The mechanism of WC cash benefits are awarded is further complicated by distinguishing between various types of injuries as scheduled vs. unscheduled. *Scheduled* injuries typically affect the upper or lower extremities and are listed as percentage of extremity; unscheduled injuries affect the spine, nervous system, or other organ systems and are awarded as a percentage of the "whole person."[41]

Although the impairment rating is the common factor in disability determinations as cash benefits, it is not the sole factor. However, in practice, many jurisdictions implement procedural shortcuts whereby the impairment rating percentage becomes a direct surrogate for the disability rating according to a predetermined formula that multiplies the impairment percentage times several weeks wages (up to a cap) times a percentage (generally two-thirds to three-fourths) of the average weekly wage (up to a cap) and resulting in a lump sum pay out. The adequacy of applying the impairment rating as an operational surrogate measure of disability continues to be a subject of debate.

Implications for pain sufferers can be noted: The metrics for medical impairment rating clearly favor and emphasize objective over subjective criteria. As such, painful entities such as headache, fibromyalgia, or low back pain often occur in the absence of objective, verifiable pathology or may present in a setting where objective clinical findings are most consistent with normal anatomic variation and the aging process and may be of little or no clinical significance to the individual's actual complaints. Impairment ratings in such cases are ineffective since minimal or no rating percentage is currently allowed in relation to any apparent (and often profound) negative impact that these conditions may be having upon ADLs. The disablement, and ensuing losses in such cases, potentially become more evident if viewed in terms of QOL. There are well respected psychometric instruments now available to measure the QOL. Notable examples include the quality of wellbeing (QWB) scale, the WHOQOL-100, and the QOL index (QLI).[42] Unfortunately, such metrics are not familiar tools to the typical rating physician and are not routinely taken into account by the rating systems per se. Consequently, losses in terms of QOL remain largely unaccounted for by the rating practice summarized above.

American Medical Association Guides

The process whereby disability determinations are made requires that an initial impairment rating be made according to standard and specific medical criteria. Since the physician is empowered and charged to render such ratings, the AMA has produced a rating manual to assist physicians in this regard. The *American Medical Association Guides to the Evaluation of Permanent Impairment (AMA Guides)* is a standardized, objective reference for this purpose, initially published in 1971 as a compilation of a series of impairment rating articles for different organ systems that were published in the *Journal of the American Medical Association* from 1958–1970. It has periodically been updated and revised to the most current *AMA Guides, sixth edition* published in 2008.[43]

The *AMA Guides* is recognized nationally and globally as the preferred reference for medical impairment ratings. Various editions are required or recommended by statute in the majority of United States WC jurisdictions. To date, the *AMA Guides, sixth edition* has recently been adopted by 19 jurisdictions in the United States and is the reference mandated by the USDOL in the various disability systems outlined above. It is also adopted and used internationally in WC and personal injury claims, including nine of ten Canadian provinces and all three Canadian territories, the Netherlands, South Africa, Australia, New Zealand, Malaysia, Korea, Hong Kong, and the Middle east. The United Nations peacekeeping operations also use the *AMA Guides, sixth edition* to adjudicate personal injury claims arising from peacekeeping mission assignments.

The *AMA Guides, sixth edition* builds upon the precedent of the previous edition of the *Guides* in placing increasing emphasis upon a diagnosis-based approach, with particular emphasis on musculoskeletal impairment ratings of the spine and extremities. Diagnosis-based impairment (DBI) grids are provided for each anatomic region (cervical spine, thoracic spine, lumbar spine and pelvis for the spine; digits/hand, wrist, elbow, and shoulder for the upper extremity; and foot & ankle, knee, and hip for the lower extremity). Each grid has five potential impairment classes (Class 0–4) consistent with the ICF classification system, and each covers a broad and precise array of diagnoses ranging from soft tissue conditions (non-specific, chronic, or recurrent) to muscle-tendon and/or motion-segment injuries (sprains, strains, tendinopathy), and to ligament, bone, and joint injuries (fractures, dislocations, arthrodesis). The impairment rating is a two-step process whereby an initial assignment to an impairment class requires the rating examiner to identify the most appropriate diagnosis. Each diagnostic-based impairment class has an available range of impairment values with an initial "default" mid-range value. The rating is then adjusted within-range as a second step, using three separate criteria to validate the diagnosis and severity (functional history, examination findings, and clinical test results) of the condition and by using a simple triangulation method enables a final numerical adjustment upward for less-favorable outcomes or downward for more optimal outcomes according to the specific result in each case.[44]

Medicolegal Constructs and Constraints

In general, the pain practitioner has unique legal liabilities that include administrative, civil, and criminal liability exposure both at the state and federal level, the discussion of which is beyond the scope of this chapter. Alternatively, a brief overview of the interaction between impairment and disability assessor and the law is indicated. The pain practitioner participating in such evaluation is encouraged to become familiar with the emerging field of disability medicine described as a sub-specialty of clinical medical practice that encompasses identifying, predicting, preventing, assessing, evaluating, and managing impairment and disability in both human individuals and populations.[45]

The IME

IME: A (usually) one-time evaluation performed by a physician examiner who is not treating the patient or claimant to answer specific questions posed by the referring party, including MMI

determination, impairment rating, and return to work restrictions, if applicable.[46]

IMEs are examinations performed by a physician who is not involved in the person's care to clarify medical and job issues. IMEs are performed to provide information to case management and for evidence in hearings and other legal proceedings. IMEs are a component of most WC statutes, although the specifics vary by state and country. They are performed at several stages during the cycle of injury/illness, treatment, rehabilitation, and return to work. The key issues associated with an IME differ from clinical consultations in role and focus. In the WC arena, IMEs may be performed any time there is a dispute, concern, or question regarding the medical treatment or condition of the injured worker. These issues include such topics as:

1. Diagnosis, proximate causation, and work-relatedness of an illness or injury.
2. Current and proposed medical treatment or diagnostic efforts.
3. Appropriate work and general activity level during treatment.
4. Stability of the medical condition and status regarding maximal medical improvement.
5. Identification of other non-medical factors that can have a significant impact on the outcome of the medical condition or treatment.
6. Impairment rating and related disability issues under certain circumstances.
7. Ability to return to work (fitness for duty) and reasonable accommodation.

IMEs can help to untangle the complex relationship between *pathology* (a medical condition or diagnosis), *impairment* (an anatomic or functional abnormality or loss), *activity limitations* (a reduction in ADLs that can be assessed by functional metrics), and *participation restrictions* (a reduction in the ability to perform socially-defined activities or roles). The opinions outlined in the IME report are expected to be expressed in terms of medical probability vs. medical possibility in all cases, where the following definitions apply:

Medical Possibility: Something could occur because of a particular cause (probability less than or equal to 50%).

Medical Probability: Something is more likely to occur than not (probability exceeds 50%).[47]

Physician Testimony and Liabilities

The IME is a form of expert witness testimony that embraces the important task of assessing a claimant's health in accordance with their legal rights, entitlement, and potential for monetary gain. The independent medical examiner, acting as an agent to the consulting party rather than as a patient advocate, also bears the risk of becoming a target for allegations of wrongdoing leveled by the disgruntled claimant.

From a legal perspective, an independent medical examiner or a disability evaluator is essentially an expert witness. As such, and until recently, the expert had enjoyed essentially the same type of immunity as to any other witness in the judicial process. This immunity from civil liability ran quite deep and included protection from claims of defamation and negligence. The witness immunity can be traced back to the 16th century English common law.[48] The idea behind witness immunity was to ensure that the witness would speak freely when giving testimony.[49] Subsequently, the American courts considered the issue of witness immunity to be so important that it was maintained even when there might be negligence.[50] Traditionally, the argument for such immunity has been that expert witnesses are an important part of the legal system, and in the interest of justice, expert witnesses need to be protected from liability. Several state courts have affirmed the concept of witness immunity for reasons of public policy because, without immunity, there would be a loss of objectivity, and the fear of infinite vexation would have a chilling effect on the witness and the reluctance to testify.[51]

The United States Supreme Court, in the 1980s, confirmed the importance of witness immunity in two cases. In *Briscoe*,[52] the court noted that a witness who knows that he might be forced to defend a subsequent lawsuit and perhaps to pay damages might be inclined to shade his testimony in favor of the potential plaintiff, to magnify uncertainties and thus to deprive the finder of the fact (judge or jury) of candid, objective, and undistorted evidence.

In *Mitchell*,[53] the United States Supreme Court reasoned that witness immunity is important because the judicial process is an arena of open conflict, and in virtually every case there is, if not always a winner, at least one loser. The court noted that it is inevitable that many of those who lose will pin the blame on witnesses and would bring suit against them in an effort to re-litigate the underlying conflict.

The continuous theme that ran through these cases emphasized that the object of immunity is not to protect those whose conduct is open to criticism but those who would be subject to unjustified and vexatious claims by disgruntled litigants. However, recent development in the law of liability of expert witnesses in the past two decades has caused many cracks in the expert witness armor.

The legal liabilities of the independent medical examiner as an expert witness are mainly grounded in legal theories (referred to in legal parlance as causes of action) of tort law and to some extent in contract law by which the injured party as a plaintiff may bring a lawsuit against a healthcare provider. It should be noted that a liability claim against a practitioner can be and is usually brought simultaneously under several legal theories. The plaintiff hopes to win under any or all of these claims leading to the recovery of a monetary award from the defendant practitioner.

Insert Table 23.2 here:

The underlying principle of the common law (both law of tort and contracts) is to provide a venue for a person who has suffered damages because of an action or inaction by others to seek redress for his or her grievance in the courtroom. The tort law has been described as a great equalizer as it gives the individual an ability to bring a potentially mightier wrongdoer (referred to in legal parlance as tortfeasor) before the bar on a more equal footing for the wrongs that may have been done to her and secure compensation for her loss. Obviously, the law cannot make the tortfeasor undo the injury or harm but makes them pay monetary compensation for both intentional wrongs (for example, defamation, assault, and battery) and unintentional (e.g. negligence). The law of tort shifts the burden of the cost of the injury or damages to the responsible party and serves to prevent similar harm to other members of society through enforced accountability. The idea is to make the offensive, and undesirable behavior costly to the tortfeasor and, in principle, serves to deter others from engaging in behaviors such as the defendant in the future.[54]

Traditionally, the healthcare provider's liability to their patients arises out of medical malpractice claims. The term *malpractice* refers to any professional misconduct that encompasses an unreasonable lack of skill or unfaithfulness in carrying out professional or fiduciary duties.[55] Under the theory of negligence, the law of

TABLE 23.2 Legal Theories of Causes of Action Against IME Doctors/Expert Witnesses

A. Intentional Tortes
1. Assault
2. Battery
3. Intentional infliction of emotional distress
4. False imprisonment
5. Defamation
6. Invasion of privacy
7. Fraud and misrepresentation
8. Conspiracy
9. Bad faith
10. Deceptive trade practices

B. Unintentional Tortes
1. Ordinary negligence
2. Professional malpractice
3. Failure to warn
4. Wrongful death
5. Loss of chance of recovery or survival
6. Vicarious liability for the acts of others
7. Negligent referral
8. Failure to diagnosis
9. Failure to inform

C. Actions Under Law of Contract
1. Breach of contract
2. Breach of warranty
3. Abandonment

D. Miscellaneous Causes of Action
1. Deceptive trade practices
2. Violation of a statute or regulation

torts is the most common basis for a medical malpractice action against a healthcare provider. However, under this action, the plaintiff must prove that the practitioner had a duty to the patient and breached that duty because of which (causation) harm or damage occurred.

Until recently, the medical malpractice actions against the IME doctors and expert witnesses failed because of a lack of doctor/patient relationship with the examinee/plaintiff.[56] The continuous theme that ran through the cases across various jurisdictions in the United States was that as long as the IME doctor neither offered to nor intended to treat the individual examinee, there was a lack of doctor/patient relationship, which prevented the medical malpractice cause of action.[57] Many potential cases were either not filed because of prevailing notions among the legal community based on the previous case law, or cases when filed were dismissed upon pre-trial motions from the defendants.[58,46–48] However, this has changed significantly in the past two decades with increasing case law from various jurisdictions holding independent medical examiners and expert witnesses accountable for the alleged harm suffered by the plaintiff/examinee. This was initially done under the cause of action of simple negligence and outside of the law of torts for medical malpractice.[49]

More recently, at least two state Supreme Courts have allowed the civil action against the IME doctors to proceed under the traditional medical malpractice theory. The legal commentators have observed that this increasing erosion of immunity from civil action for the independent medical examiner as an expert witness is because of the proliferation and growth of the litigation/expert witness industry, as well as the courts' perception of lack of protection of injured party from unscrupulous witnesses and the inadequacy of the traditional safeguards against expert witness malfeasance from potential prosecution for perjury and inadequate cross examination.

The beginning of this trend of judicial hostility toward expert witness immunity can be traced back to the mid-1990s when the state courts in the United States started holding independent medical examiners and expert witnesses without any doctor/patient relationship accountable to their examinee in ordinary negligence. This trend began in Colorado with the *Greenberg*[59] case. Several other jurisdictions have since followed. The Virginia Supreme Court in *Harris*[60] held as a matter of the first impression (making new precedent) that a doctor could be sued for malpractice for the negligent performance of a doctor's mental and physical examination of a party during an IME.

Similarly, the Court of Appeals in Arizona in the *Stanley*[61] case found that a formal doctor/patient relationship is not the only source of a doctor's duty toward a patient and that the doctor owed a duty of care to the patient despite the absence of a formal doctor/patient relationship. The Arizona Supreme Court took it a notch further in *Ritchie*[62] and allowed for medical malpractice to go forward despite no doctor/patient relationship, essentially stating that the court can envision no public benefit in not holding a doctor accountable to a duty to conform to the legal standard of reasonable care.

As can be seen from above, under case law of various jurisdictions in the United States, the expert witnesses' (as well as IME doctors') immunity, traditionally enjoyed up until recently against various legal causes of action, is now rapidly eroding. The news from the other side of the Atlantic is even worse. In a recent decision by the United Kingdom Supreme Court in *Jones*,[63] the United Kingdom Supreme Court practically stripped the expert witness from all immunities that are available to the fact witnesses, generally. After a lengthy discussion, the majority of the Jones court concluded that they see no public policy reason to justify immunity for the expert witness. While this recent decision in the United Kingdom has no authority in the United States jurisprudence, it is nonetheless regarded by some as a persuasive argument.

In summary, the pain practitioner should be aware of the legal liabilities in the overall practice of their subspecialty and the additional liabilities entailed with exposure to independent medical examinations and expert witness work. Even though the recent case law in some jurisdictions has significantly removed the traditional immunity from medical malpractice claims against providers with no doctor/patient relationship with their examinees. In American jurisprudence, there remains a great need for expert medical witness service. Practitioners attracted to disability assessment and inclined to serve as independent medical examiners are encouraged to attend several of the high-quality training programs offered in the United States to independent medical examiners and expert witnesses to empower them with the knowledge, skills, and abilities necessary to practice as an independent medical examiner and/or expert witness in the field of disability medicine.

Implications for Disability Assessment of Chronic Pain

An important point of this chapter can best be made by drawing into focus the distinction between impairment ratings and disability ratings as they pertain to the issue of pain. The construct of impairment is conceptually and operationally grounded in

the medical model of disease discussed earlier. Impairment is codified and systematically defined according to a predetermined set of objective and measurable criteria for each organ system. Conditions that affect one or more organ systems and manifest themselves in terms of objective, measurable organ system pathology are infinitely ratable according to these organ systems. The painful experience that often accompanies specific pathology can and should be accounted for in some systematic manner and included in such ratings. However, pain can occur in the absence of observed pathology specific to the organ system, and chronic painful conditions transcend the organ system boundaries of the individual and can perhaps be best described and understood in terms of the biopsychosocial model described above.[54,64]

Global pain or other chronic painful conditions not attributable to any specific organ system pathology according to the impairment rating method alluded to above can perhaps be more adequately accounted for by adopting and applying QOL measures.[65] Such metrics have the necessary empirical foundation from which to develop standards for losses in terms of non-vocational function, life satisfaction, and burden of care and medical compliance needed to maintain optimal function in the presence of chronic pain and other disabling conditions. Such metrics, when properly applied, can and should enable modification of any disability payment as a percentage add-on or standalone cash award according to specifications of each disability system. Perhaps the disabling consequences of chronic painful conditions can be more favorably captured in overall disability determinations at the point of final integration of the impairment rating, functional outcomes, and other relevant disability criteria as evidenced through such QOL assessments.

QOL measures are important factors in determining impairment and ultimately disability, as pain is a subjective experience and thus hard to quantify outside of the patient's description. Pain affects all aspects of life, which in the long term increases depression and anxiety. This is underscored by the fact that many of the patients with chronic pain do not seek out a physician's help because their pain cannot be relieved. Therefore it is important to make the experience of pain easier to bear, and QOL measures allow a validated approach to reach that goal and assess a patient's function in the context of their illness.[66]

When choosing a QOL measurement tool, it is important to determine the objective of the tool. Some tools are very narrow in their measurement and only examine certain aspects of a patient's life, such as those that measure health-related QOL, which the CDC defines as "an individual's or group's perceived physical and mental health over time." Others are disease specific such as the gastrointestinal QOL index (GIQLI), the asthma quality of life questionnaire, and the stroke specific QOL scale.[67] It is important to note that these questionnaires examine the patients' QOL in the context of the disease rather than examining the patients' overall QOL, which can be a limitation in assessing the true QOL of the patient.

Some QOL measurement tools are very broad, and rather than looking at the QOL from the standpoint of disease, examine the patients' QOL holistically. The downside to such a QOL measurement is that it can be difficult to administer because of the potential for large question numbers and length of completion. To counteract that and still measure a patient's general QOL, several QOL tools have been developed using data from the larger tool items to create smaller, easier to use ones. One such example is the medical outcome study short-form 36 (MOS SF-36). This tool measures eight aspects of the patient's life over 36 questions.[68]

Because of QOL being influenced by cultural and societal values, some measurement tools also account for those. An example of such a tool would be the World Health Organization's QOL instrument developed by the World Health Organization. This tool seeks to create a QOL evaluation that spans different cultures and languages. It covers six total domains: physical capacity, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs. To allow the cross cultural application, it allows additional questions that apply to the culture to which the patient belongs. This helped to produce a 100 questions test called the WHOQOL-100.[69] A shorter version was also developed called the WHOQOL-26 BREF, which is shorter and maybe more practical to administer. It should be noted that there are other QOL measures that are used in clinical trials. These are discussed in Chapter 84.

The use of a suitable QOL as a tool for disability assessment of pain must recognize that a valid disability assessment of pain may require a skill set and applied metrics beyond those typically embodied by the physician disability examiner. Until this ideal can be more closely achieved, the role of pain as a contributor to disability can be most properly accounted for in two ways:

Pain directly affecting impairment can be viewed in terms of functional outcomes accompanying specific impairment, as it is now possible, using the DBI approach outlined above for impairment rating as put forward in the *AMA Guides, sixth edition*, to modify the "expected" impairment rating upwards using a functionally-based "grade modifier" sensitive to pain and other limiters of function, to award additional impairment for pain-associated loss of function.

Alternatively, in cases where a specific diagnosis is lacking, and pain appears to be the primary problem, the *AMA Guides, sixth edition* currently offers a "stand alone" assessment of pain that awards up to 3% loss to the whole person where pain is not effectively rated elsewhere. Additional work is needed to perfect our current disability infrastructure to further enhance the relevance, validity, and reliability of medical impairment ratings and provide alternative metrics to expand and modify disability determinations to properly account for functional losses because of chronic pain.

Resources Available to the Physician Disability Examiner

Several educational venues and reference resources are available to enable interested physicians to gain the additional necessary knowledge, expertise, and credentials to perform impairment ratings, disability evaluations, and IMEs competently and authoritatively. These include training programs, credentialing, and certification by examination, as well as several reference texts as listed below:

1. American Board of Independent Medical Examiners: www.abime.org
2. American College of Independent Medical Examiners: www.acime.org
3. American College of Occupational and Environmental Medicine: www.acoem.org
4. American Medical Association: www.ama-assn.org

Key Points

- A pain specialist must understand the impairment and disability system they will be working with to be successful.
- Historically, there have been systems in place to provide for those unable to work because of disability. These date back to biblical times and continue into the present with various laws at state and federal levels, including social security and WC and compensation for personal injuries arising out of the negligence of others.
- State WC has three kinds of benefits: medical and rehabilitation expenses, wage loss benefits, and survivor benefits.
- State tort law allows for monetary awards for both mental and physical damage, given that it can be proven that another was at fault.
- Federal worker's compensation systems are governed by the USDOL with administration done by the OWCP (a subagency of the USDOL) and include FECA, Longshore and Harbor WC Act, Energy Employees Occupational Illness Compensation Act, Federal Black Lung Program, DBA, NAFIA, OCSLA. The other federal laws not under USDOL providing compensation include FELA (Railroad Worker Act and the Jones/Merchant Marine Act).
- SSDI covers those who are disabled because of a medically determined physical or mental impairment that lasted or likely to last greater than 12 months or end in death.
- SSI provides income for those below the poverty line who are blind, disabled, children, or older than 65 years.
- Eligibility for veterans' benefits is based on how the veteran was discharged and whether the disability was service connected, nonservice connected, or presumptive service connected.
- Private disability insurance are usually group policies and available through the workplace. They are split into short term (three months) and long term (two to three years) before reevaluation for lifetime benefits.
- The "medical model" of disability defined disability as being because of underlying pathology from illness or disease and relied on diagnosis and treatment of pathology. The "social model" of disability defines disability as the failure of society to address the disabled individual's special needs regarding priority awareness, environmental access, and infrastructural accommodation for major life activities.
- The ICIDH considered a disability to be four linear linked domains: pathology, impairment, disability, and handicap. The ICF, which replaced it, focused on an interactive association between an individual and their disability, including the functional consequences of their impairment and the context of personal versus environmental nature. ICF focused on activity, participation, impairments, activity limitations, and participation restrictions.
- Pain medicine practitioners should focus more on QOL measures, and the tools available are helpful when evaluating chronic pain and resulting impairment and Disability.
- The *AMA Guides* are essential to describing an impairment in many legal jurisdictions.
- One key difference between independent examiners and everyday patient interactions is that there is no patient-physician relationship between an independent medical examiner and the examinee.
- There are multiple ways to become proficient in medicolegal and disability ratings, particularly training courses.

Suggested Readings

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PART 4

Clinical Conditions: Evaluation and Treatment

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Chronic Post-surgical Pain Syndromes: Prediction and Preventive Analgesia

NANTTHASORN ZINBOONYAHGOON, YUN-YUN K. CHEN, KRISTIN L. SCHREIBER

Introduction

Chronic post-surgical pain (CPSP) is a growing area of study in pain medicine.[1] An increasing number of patients undergoing surgery each year,[2] multiplied by a variable reported incidence (5%–85%),[3] produces an increased number of patients with new chronic pain. In recognition of CPSP as an important global health problem, the International Association for the Study of Pain (IASP) named 2017 the Global Year Against Pain After Surgery.[4] In the upcoming International Classification of Disease (ICD-11), which is expected to be implemented in January 2022 by the World Health Organization, CPSP is recognized as one of the seven major types of chronic pain (MG 30.XX) under distinct codes for "chronic postsurgical pain" (MG 30.21), "chronic postsurgical or posttraumatic pain, unspecified" (MG30.2Z), and "other specified chronic postsurgical or posttraumatic pain" (MG30.2Y).[5,6] CPSP is a distinct subset of chronic posttraumatic pain, the definition of which is "pain developing or increasing in intensity after a tissue injury (involving any trauma including."[6] The code for chronic posttraumatic pain also includes persistent pain after trauma, spinal cord injury, nerve injuries, and burn injury.[6]

Publications regarding CPSP have grown exponentially over the last decade, from 178 publications by 2009 to 938 publications by 2019,[7] providing a strong but heterogeneous and complex body of evidence. This chapter will cover the definition, incidence, and proposed pathophysiology of CPSP, summarize what is known about potential risk factors that may aid prediction, and outline strategies for preventive efforts.

Definition of CPSP

The concept of CPSP is pain that lasts longer than the physiologic healing process after surgery. Simple diagnostic criteria for CPSP were proposed by Macrae[8] in 2001 as pain developing after a surgical procedure of at least two months duration, with other causes for the pain having been excluded (e.g. continuing malignancy or chronic infection), including the possibility that the pain continues from a preexisting problem. However, there have been additions and modifications to this simple definition, including:[9]

1) Many patients already experience pre-surgical pain. To define CPSP for patients who already had pre-surgical pain, post-surgical pain should have increased severity and/or be accompanied by a change in location or character.
2) The duration of two months may be too short to be considered as chronic pain in some cases, and thus the required duration of pain should be extended to at least three–six months.
3) Rather than simply categorizing pain as absence/presence, pain severity and impact should be considered, with CPSP defined as pain that the patient feels has at least a minimal impact on quality of life.
4) CPSP commonly develops immediately after surgery but may also develop after a pain-free period, possibly because of the delayed onset of neuropathic pain after nerve injuries (inguinal hernia repair, breast surgery with axillary dissection).
5) The CPSP may involve locations outside the surgical site. For example, patients suffering from persistent pain after breast cancer surgery report pain not only at the breast or axilla, both in the upper medial arm,[10] likely because of intercostobrachial neuralgia from axillary node dissection.[11]

IASP updated the definition of CPSP in 2017:[12] "Chronic post-surgical pain is chronic pain developing or increasing in intensity after a surgical procedure and persisting beyond the healing process, i.e. at least three months after surgery." The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome (after surgery/injury to deep somatic or visceral tissues). Other causes of pain, such as infection and malignancy, need to be excluded, and pain continuing from a preexisting pain problem. Depending on the type of surgery, CPSP often includes elements of neuropathic pain (Table 24.1). These newly proposed criteria provide a more comprehensive picture of CPSP and may be used as diagnostic criteria in the ICD-11 coding system.

Incidence of CPSP

Having a well-developed definition and standard diagnostic criteria has assisted the visibility and recognition of CPSP, which had previously been underestimated.[13] However, the diagnostic criteria for CPSP do not specify a clinically meaningful pain severity to define CPSP. Even with these more closely defined diagnostic criteria, variation in cut points for the severity constituting clinically significant pain and at timepoints chosen to study CPSP likely contributes to the wide range of reported incidence of CPSP in the literature. Studies have used different definitions to denote clinically meaningful CPSP, ranging from anything >0/10 on the pain scale to only considering pain >3 or >4/10 as significant.[10] Frequency may be variable (constant vs. intermittent), and the

TABLE 24.1 Evolution of the Definition and Diagnostic Criteria of Chronic Post-surgical Pain

Macrae 2001[8]	Werner and Kongsgaard 2014[9]	IASP 2019[6]
(1) The pain should have developed after a surgical procedure. (2) The pain should be of at least two months duration. (3) Other causes for the pain should be excluded, e.g. continuing malignancy (after surgery for cancer) or chronic infection. (4) The possibility that the pain is continuing from a preexisting problem should be explored, and exclusion attempted. (There is an obvious grey area here in that surgery may exacerbate a preexisting condition but attributing escalating pain to the surgery is clearly not possible as natural deterioration cannot be ruled out.)	(1) The pain develops after a surgical procedure or increases in intensity after the surgical procedure. (2) The pain should be of at least three to six months' duration and significantly affect the HR-QOL. (3) The pain is either a continuation of acute post-surgery pain or develops after an asymptomatic period. (4) The pain is either localized to the surgical field, projected to the innervation territory of a nerve in the surgical field, or referred to a dermatome (after surgery in deep somatic or visceral tissues). (5) Other causes of the pain should be excluded, e.g. infection or continuing malignancy in cancer surgery.	The pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, i.e. at least three months after the initiating event. The pain has to be localized to the surgical field or area of injury, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome or Head's zone (after surgery/injury to deep somatic and visceral tissues). Other causes of pain, such as preexisting pain conditions or infections, or malignancy, have to be excluded in all cases of chronic posttraumatic and post-surgical pain.

quality of the pain may depend on its location and the exact mixture of its mechanistic basis. From mild to debilitating pain, this range of severity correspondingly results in varying degrees of negative impact on quality of life.[14]

Thus the estimates for the incidence of CPSP vary substantially even among studies using the same procedure (Table 24.2),[15,16] according to the methodologic differences in defining CPSP by pain intensity (Table 24.2),[6] and by time (Fig. 24.1), and across study samples.[16] The procedures with the highest reported incidence of CPSP include thoracotomy (5%–65%), mastectomy (11%–57%), and amputation (30%–85%). These procedures also have a higher prevalence of moderate to severe pain (5%–10%) than herniotomy (2%–4%)[12] and seem to have more neuropathic characteristics (66%–68% for thoracotomy and mastectomy) than hip or knee arthroplasty (6%).[15]

TABLE 24.2 Incidence of Chronic Post-surgical Pain by Operation and Pain Intensity and Proportion of Neuropathic Pain

Type of Surgery	Incidence of All CPSP	Incidence of Severe CPSP (>5/10 of 10/10)	Proportion of Neuropathic Pain in CPSP
Amputation	30%–85%	5%–10%	80%
Cesarean delivery	6%–55%	5%–10%	50%
Cholecystectomy	3%–50%	Not reported	Not reported
Coronary bypass	30%–50%	5%–10%	Not reported
Craniotomy	7%–30%	25%	Not reported
Dental surgery	5%–13%	Not reported	Not reported
Hip arthroplasty	27%	6%	Not reported
Inguinal herniotomy	5%–63%	2%–4%	80%
Knee arthroplasty	13%–44%	15%	6%
Melanoma resection	9%	Not reported	Not reported
Mastectomy	11%–57%	5%–10%	65%
Sternotomy	7%–17%	Not reported	Not reported
Thoracotomy	5%–65%	10%	45%
Vasectomy	0%–37%	Not reported	Not reported

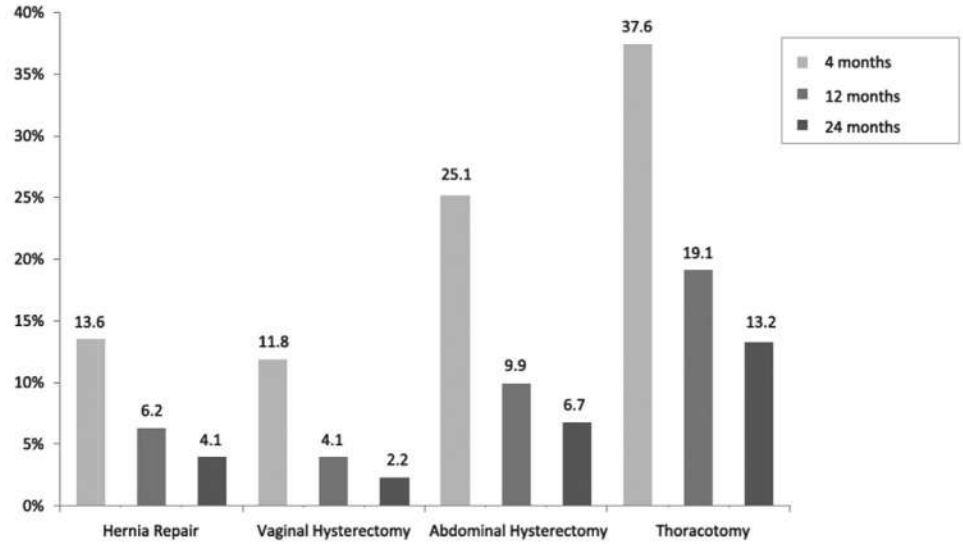
With permission from Schug et al.[12]

Although cross-sectional studies are the most common, some longitudinal studies have tracked the incidence of CPSP at later time points and generally show a decrease over time. For example, the incidence of CPSP after thoracotomy in the study by Montes et al. showed 38% at four months, 19% at 12 months, and 13% at 24 months.[16] A similar mean trajectory of CPSP has been reported after hysterectomy and hernia repair (Fig. 24.1).[16] In contrast, other studies have suggested a relatively low but stable incidence beyond three months, as in the case of mastectomy, where both cross-sectional studies querying patients at six months to six years,[17] and longitudinal studies out to 12 months,[18] suggest a similar incidence of about 30% reporting pain of ≥3/10 or more. A more in-depth analysis, taking interpatient variability into account, suggests that there may be multiple pain trajectories within the first year after surgery, depending on severity, experienced by different subgroups of patients.[19]

A large international study averaging across multiple surgical types showed an overall incidence of CPSP of 41% (95% CI 38–43) at six months and 35% (95% CI 32–39) at one year. However, patients with severe pain (NRS ≥6/10), who also reported greater pain interference with activities and mood than patients with more moderate pain, represented only 2% of patients in the same study (95% CI 1–3).[14]

Proposed Mechanisms of CPSP

Surgical injury leads to acute postoperative pain that may be nociceptive, inflammatory, and/or neuropathic when viewed according to classic pain categorizations. However, the exact mechanism(s) involved in the pathophysiology leading to the maintenance or chronification of post-surgical pain is not well established and may vary according to *nature* of the injury and tissues involved. Three important mechanistic concepts that may be important for understanding the chronification of pain after



• **Figure 24.1** Incidence of chronic post-surgical pain after hernia repair, hysterectomy, and thoracotomy at different time points after surgery. With permission from Montes et al.[16]

surgery include neuroplasticity, nerve injury, and opioid-induced hyperalgesia.

Neuroplasticity

Neuroplasticity is a term that describes the adaptability within the structure and function of the nervous system, a quality that fundamentally underlies several crucial tasks of the nervous system, such as learning and memory, and also includes self-preservation from noxious stimuli.[20] The intense nociceptive and inflammatory stimuli from tissue injury that occurs during surgery is a message that the nervous system cannot evolutionarily afford to ignore. The nervous system response to tissue injury can be regarded as functional neuroplasticity. Increased pain immediately after surgery can drive adaptive behaviors that facilitate healing. However, these processes, when sustained or solidified into CPSP, represent a maladaptive change.

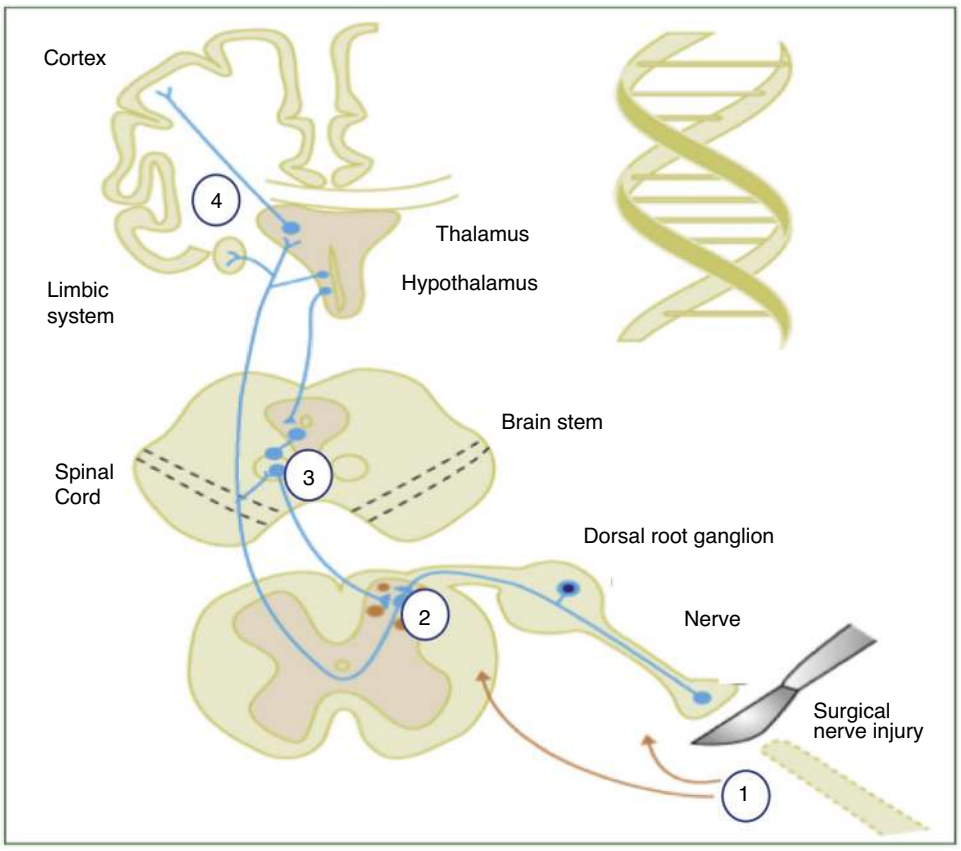
Surgical injury of tissues leads to a local release of inflammatory and other mediators and creates an acidic and often locally ischemic environment. These mediators activate peripheral nociceptors both directly through binding of mediators and by decreasing the threshold to activation by other stimuli, making normally painful stimuli more painful (hyperalgesia) and painful nonpainful stimuli (allodynia) at the site of injury (primary hyperalgesia and allodynia, limited to injury site).[3] intense and maintained nociceptive input from the periphery also activates central nociceptive pathways, starting at the level of the dorsal horn,[21] and modulating descending facilitation and inhibition from supraspinal centers,[22] and cortex.[23] This multi-level activation contributes to increased sensitivity at the primary site and sites distal to the injury (secondary hyperalgesia), otherwise known as central sensitization (Fig. 24.2).

Changes in receptor and gene expression in the dorsal root ganglion contribute to this prolonged excitability of primary nociceptors (peripheral sensitization) and thus enhanced transmission of the nociceptive signal.[3] Correspondingly, the continued transmission of this nociceptive input can cause transcriptional changes at the level of the spinal cord that underlie central sensitization.[3] The *N*-methyl-D-aspartate (NMDA) receptor plays a pivotal role in the amplification of pain and central sensitization at the level of the spinal cord, as evidenced in pre-clinical and human models.[24] The application of NMDA receptor antagonists to prevent hyperalgesia in experimental models[25] provided hope for a similar outcome in humans. Some studies showed that NMDA receptor antagonism with agents such as ketamine might modify the incidence or intensity of CPSP in clinical application.[26] Additionally, the response from surrounding immune, stromal, and glial cells in the periphery and spinal cord causally contributes to and sustains peripheral and central sensitization, influencing the extent and duration of pain and its transition to a more chronic state.[3] In keeping with the idea of noxious nociceptive input from the periphery driving central sensitization, efforts to interrupt the intense nociceptive signal have long been viewed as a way to prevent pain amplification and nervous system plasticity (preventive analgesia, sometimes called preemptive analgesia).

The concept of preemptive analgesia was described in 1983 as an early analgesic intervention initiated before a nociceptive stimulus, which may "preempt" the development of persistent pain.[27] However, clinical studies comparing analgesics given before vs. immediately following an injury failed to strongly confirm the idea of preemption.[28] The subsequent concept of preventive analgesia recognized the need to extend the time window of intervention to cover not only the initial intense nociceptive stimulation (during injury or hours after injury) but also the ongoing inflammation and aberrant firing of injured nerves at later time points (days after injury), when ongoing nociception has not yet abated.[29,30] The impact of regional anesthesia (nerve blocks),[31] and pharmacologic agents such as ketamine,[26] and lidocaine,[32] have been often studied, with mixed but promising results in preventing CPSP. The definitions of these concepts are summarized in Table 24.3.

Opioid-Induced Hyperalgesia

Opioids have long been commonly used as potent analgesics. However, when used chronically and at high doses, analgesic efficacy may diminish, disappear, or even lead to increased pain. This paradoxical phenomenon, where opioids lead to a hyperalgesic state, is called opioid-induced hyperalgesia.[36]



• **Figure 24.2** Sites and possible mechanisms responsible for chronic post-surgical pain: (1) Tissue and nerve injuries signal intense pain stimuli and peripheral sensitization; (2) changes in the sensitivity in the dorsal root ganglion producing central sensitization; (3) brainstem descending controls modulate pain transmission in spinal cord; (4) limbic system, hypothalamus, and cortex contribute to altered mood and behavior. Modified with permission from Kehlet et al.[3]

TABLE 24.3 Terms and Definitions

Term	Definition
Preemptive analgesia	An intervention initiated before a nociceptive stimulus, aimed at significantly decreasing or eliminating the nociceptive stimulus to the point that it does not lead to central sensitization and prolonged pain.[30,33]
Preventive analgesia	An intervention that is initiated before a nociceptive stimulus and continues until the majority of nociceptive stimuli have abated.[30,34]
Peripheral sensitization	Changes in the peripheral nociceptor and its milieu that lower the pain threshold and lead to a greater response for any given stimulus.[30,35]
Central sensitization	Changes in the central nervous system at the level of the spinal cord or higher that result in pain hypersensitivity.[3,30]

Opioid-induced hyperalgesia (OIH) can be conceptualized as secondary hyperalgesia. The mechanism underlying OIH likely involves transcriptional changes leading to an imbalance between pro and antinociceptive pathways,[37] including μ-opioid signaling, pronociceptive ion channel modulation, and microglial activation.[38] Chronic exposure to opioids has been shown to result in μ-opioid receptor phosphorylation by G-protein coupled receptor kinases, which leads to β-arresting-2 recruitment, μ-opioid receptor endocytosis, and receptor unavailability.[38,39]

A systematic review of clinical studies suggests that high intraoperative doses of remifentanil are associated with small but significant increases in acute pain after surgery. [40] Even lower dose and briefer exposures to remifentanil (0.1 mcg/kg/min for 30 min) have been associated with OIH.[41] In pre-clinical studies, the hyperalgesic effect of a single dose of fentanyl can last for three weeks.[36] OIH may potentially augment hyperalgesia from tissue injuries itself, making opioid-sparing strategies such as multimodal analgesia especially important in treating both acute postoperative pain and CPSP. Ketamine, an NMDA receptor antagonist, has been shown to decrease β-arresting-2 transcription in mice[42] and to clinically decrease punctate hyperalgesia in humans who received remifentanil.[41] Within a clinical context, it may be challenging to distinguish OIH from opioid tolerance, inadequate analgesia, and changes in underlying disease pathology. However, it may be suggested by altered sensory processing such as allodynia and hyperalgesia and worsening pain with further doses of opioids.[38] Assessing specifically for signs of OIH early after surgery may allow a better determination of the extent to which OIH contributes to CPSP.

Nerve Injury

Peripheral nerves are among the tissues that can be injured by surgery. Peripheral nerve injury is often considered a central contributor to the mechanistic basis of CPSP. As outlined in the

neuroplasticity section above, peripheral nerves contribute fundamentally to carrying an augmented message of pain after any tissue injury, whether the nerves themselves have sustained structural damage. However, pre-clinical studies have shown that a variety of damage to peripheral nerves may cause increased and spontaneous firing of action potentials, changes in gene expression including up and downregulation of neurotransmitters, and immune system activation after injury. These changes occur at the dorsal root ganglion level but reverberate to the dorsal horn and higher centers.[3]

Neuropathic pain in the context of CPSP can be defined in various ways, although typically utilizing questionnaires such as the DN4, S-LANSS, and painDETECT, or by including similar questions in a surgery specific questionnaire.[43] The presence of pain features of a certain quality (e.g. burning, tingling, stabbing) are indicators of nerve injury. Based on these definitions, the prevalence of neuropathic pain in CPSP varies from 6% to 68% among various surgeries,[15] although the highest reported ranges appear after thoracic and breast surgery and lowest after hip or knee replacement.[15] While more extensive nerve damage is associated with a higher incidence of CPSP,[3] higher pain severity,[44] and functional impairment,[14] nerves are rarely injured in isolation, and causation cannot be inferred from this correlation.

Risk Factors and Prediction of CPSP

Many putative factors have been linked to the incidence of CPSP and its severity, impact, and related complications, such as persistent opioid use. These factors may allow further insight into the mechanism underlying CPSP and have been put to practical use to estimate the risk of CPSP in many predictive models.

Risk Factors for Developing CPSP

Although surgical injury, by definition, is the inciting event for CPSP, the surgical extent is not always the best predictor of greater incidence and severity of CPSP. Chronic pain is a complex interaction between nociception and an individual's life. Many factors beyond the degree of tissue injury are formative to the individual experience of pain after surgery, including genetic, psychological, and social factors. The biopsychosocial model of pain, which includes biophysical differences between individuals (genetic variation, baseline nociceptive sensitivity, opioid dependence), and differences in psychosocial factors known to be involved in the processing of pain (anxiety, depression, coping strategies, social support), provides a comprehensive picture of the risk and predictive model for CPSP (Fig. 24.3).

Surgical Factors

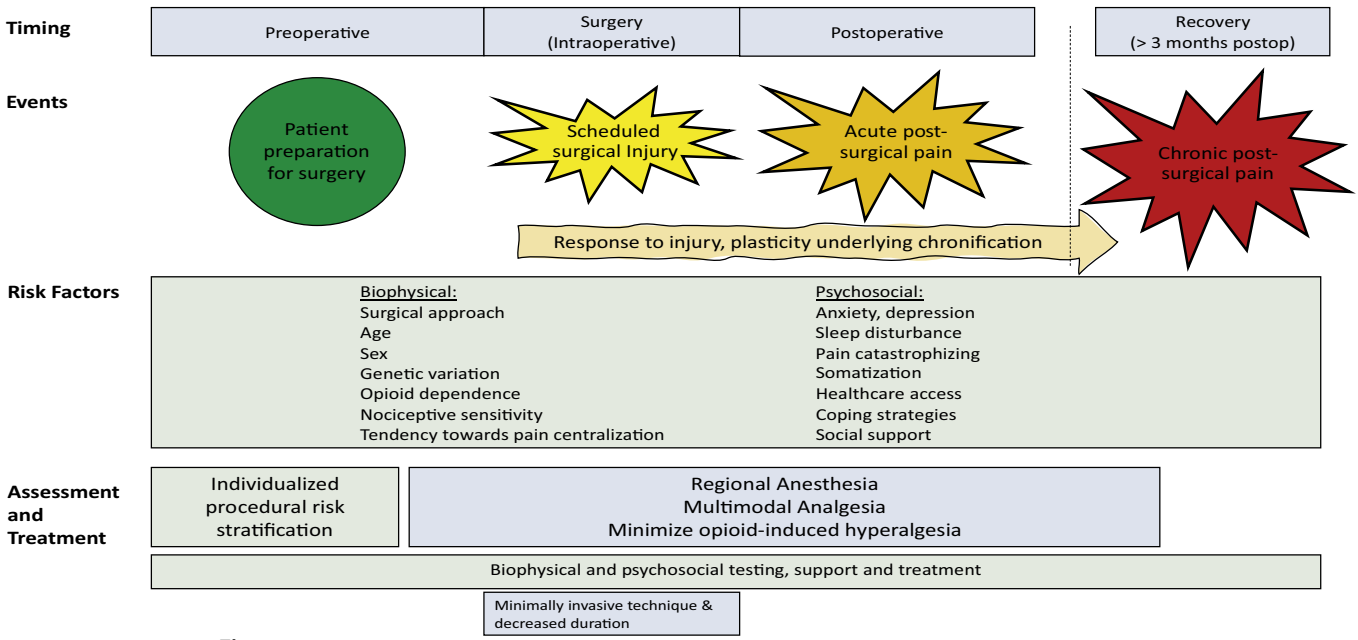
Tissue and nerve injury in each procedure must also be considered as part of the biologic variation that occurs between individuals undergoing surgery. Certain procedures are associated with different ranges of CPSP incidence,[12,16] typically with procedures of greater extent associated with higher rates. Surgical factors associated with CPSP include longer duration of surgery, low (vs. high) volume of surgical center, open (vs. laparoscopic) approach for some operations such as inguinal hernia repair,[46–48] and intraoperative nerve damage.[21]

Tissue injury is not necessarily limited to the initial surgical injury. For example, patients who underwent repeated inguinal hernia repair were more likely to develop moderate or severe pain.[49] Similarly, and patients who received radiotherapy after breast cancer surgery had a higher likelihood of CPSP in a meta-analysis (odds ratio [OR] = 1.35[1.16–1.57]),[50] possibly because of the increased incidence of tissue fibrosis, neural entrapment, and impaired glenohumeral motion.[51]

Patients Characteristics

Age and Sex

Younger age and female sex are associated with an increased risk of CPSP.[12,21] A multivariable analysis by Montes et al. found that, compared to older patients (>64 years), younger patients had a greater incidence of CPSP (OR 3.1 [2.4–4.0] for 18–50-year-olds, and OR 1.6 [1.2–2.1] for 51–64 patients).[16] Similarly, in a meta-analysis of 30 studies involving 19,813 patients undergoing breast cancer surgery, the absolute risk of CPSP increased 7% [5%, 9%] for every ten years decreased from age 70.[50]



• **Figure 24.3** The comprehensive risk factors in the biopsychosocial model for developing chronic post-surgical pain. Chen Y-YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic post-surgical pain: a narrative review. *Anaesthesia*. 2021;76(1):8–17.[45]

Preoperative Pain

Preexisting pain at the surgical site represents sensitization of nociceptors in the area,[21] and further nociceptive input from surgical injury likely further augments this sensitization in an additive or supra-additive fashion.[49] Chronic pain in nonsurgical areas is also an important risk factor, indicating a tendency toward amplification of the pain signal over endogenous pain inhibition,[16,52] or central sensitization.[53] Other studies have associated longer duration and higher intensity of preoperative pain with the development and persistence of CPSP.[21,54] One study reported a slightly higher risk of CPSP for preoperative pain at the surgical site than preoperative pain at a remote site. However, both surgical site and generalized pain appear to be robust predictors of CPSP.[52] A multivariable analysis from a large observational multinational study showed the presence of chronic preoperative pain at any site is the strongest predictor of CPSP at 12 months after surgery (OR 1.89 [1.12–3.18]).[14] Preoperative pain, either at the surgical site or chronic pain at another site, are consistently included among the key predictors in most prediction models for CPSP.[14,16,18,54–56]

Preoperative Opioid Use

Long term opioid use for the treatment of chronic pain may increase the risk of CPSP, either as a marker of preoperative chronic pain severity or OIH, or both.[57] However, whether opioid use serves as a causal contributor to CPSP or is simply a common coincidental finding because of chronic pain is still unknown. In one cohort study, preoperative opioids were associated with CPSP on a simple univariable analysis (relative risk [RR] 2.0 [1.2–3.3]). However, when other factors, including preoperative pain status, were included in the multivariate analysis, preoperative opioid use was no longer a significant predictor (RR 1.3 [0.8–1.9]).[58]

Psychological and Social Factors

The experience of pain involves a complex interaction between nociception and psychology. The impact of psychological factors on acute postoperative pain, CPSP, and other types of chronic pain is well documented. An earlier meta-analysis indicated an important association of psychological factors including depression, psychological vulnerability, and stress with CPSP after various surgeries, including thoracotomy, mastectomy, hernia repair, and orthopedic surgery.[59] Then an even broader investigation of psychological factors including both state and trait anxiety or depression, pain catastrophizing, sleep disturbance, somatization, positive and negative affect, coping strategies, and expectations found an association of higher psychological distress with greater incidence and severity of CPSP.[10,17,60–63] In particular, pain catastrophizing, defined as a tendency to magnify, ruminate, or feel helpless in the face of painful sensations,[62] has proven an interesting and consistent correlate of CPSP,[17,61] and chronic pain generally.[64] A meta-analysis showed a strong association between pain catastrophizing and CPSP (pooled OR of the minimum effect of 2.13 [1.26, 3.59]).[61] Psychological factors can be assessed perioperatively with validated questionnaires such as the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) short forms for depressive symptoms, anxiety, and sleep disturbance,[65] the Brief Symptom Index (BSI)-Somatization Scale for somatization,[66] or questionnaires such as the Pain Catastrophizing Scale.[67]

Social and sociodemographic factors may also influence pain experiences, including resources and access to care. Socioeconomic factors and disability status have been variably implicated as risk factors in systematic reviews and meta-analyses.[12] Lower educational and employment status have been associated with vulnerability to developing chronic pain.[68–71] The contribution of social factors to CPSP risk has been understudied compared to biologic and psychological constructs.[72] However, social interactions appear to also play an important role in modulating pain and the ability to cope with chronic pain,[73] although the interaction of social and psychological factors, both complex and difficult to study, may also be important. Several studies suggest that a more insecure attachment style is associated with greater distress, lower self-efficacy to decrease pain, greater pain catastrophizing, more disability because of pain, and greater pain sensitivity.[74]

Acute Postoperative Pain

Greater nociceptor activation leads, on the one hand, to more severe acute pain, but also to a greater likelihood of central sensitization, which may contribute to the development of CPSP.[14,16] Thus greater acute postoperative pain is cited as a risk factor in many studies and is often included in models of CPSP prediction.[14,50,56] In one meta-analysis, acute postoperative pain severity was associated with an OR of 1.16 [1.03,1.30] and an absolute risk increase of 3% [1%, 6%] for every 1-cm increment on a 10-cm visual analog scale.[50] Besides acute pain severity per se, the percentage of time in severe pain on day one after surgery has also been shown to be strongly associated with moderate to severe pain from CPSP (NRS ≥3/10) at 6 and 12 months after surgery (Fig. 24.4).[14]

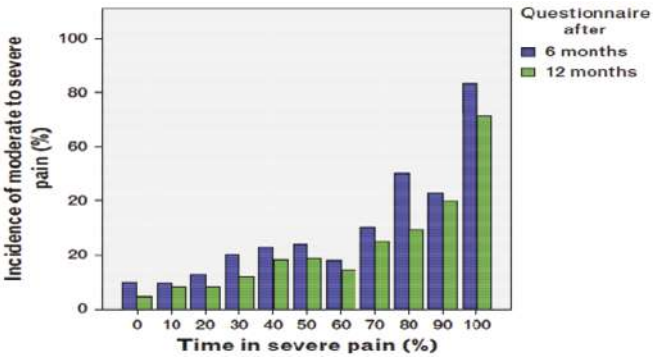
However, the severity and daily duration of acute postoperative pain may also be viewed as reflecting patient susceptibility to pain amplification, which also underlies the propensity toward central sensitization and the development of CPSP.[14] Acute pain is less of a *predictor* than a *temporal correlate* of the same process involved in the development of CPSP.

It is yet unclear whether adequate or inadequate perioperative analgesia could meaningfully affect CPSP development,[3] and in light of the goals of providing analgesia in the perioperative period, this principle may be difficult or unethical to prove. Provision of excellent acute postoperative pain control leads to a better experience for the patient, both in terms of satisfaction and perioperative recovery,[75] independent of whether it may prevent CPSP.

Other Factors

Genetic Variations

Clinical and pre-clinical studies have linked genetic factors to chronic pain. Many single nucleotide polymorphisms (SNPs), including catechol-O-methyltransferase (COMT), GTP cyclohydrolase 1 (GCH1), and DA receptor 2 (DRD2), have been linked with the risk of CPSP,[76]



• **Figure 24.4** The incidence of moderate to severe chronic post-surgical pain (≥3/10) at 6 and 12 months and the percentage of time in severe pain at postoperative day one. With permission from Fletcher et al.[14]

but a definitive genetic profile of elevated CPSP is still the object of much ongoing research. One analysis of a larger set of 90 SNPs, including those aforementioned, selected based on functional genetic variants associated with pain sensitivity and chronic pain conditions, failed to show significant differences in allele frequencies between patients with and without CPSP.[16] However, this is likely to be an area of continued interest, particularly as larger collaborative studies emerge.

Quantitative Sensory Testing

Quantitative sensory testing (QST) of an individual's response to standardized pain stimuli may help to characterize overall pain susceptibility.[77] Many studies have shown the predictive value of QST for CPSP after thoracotomy,[52] shoulder surgery,[78] and mastectomy.[10] Nevertheless, the application of QST in the clinical setting is still limited, and a relatively small pool of studies have investigated the predictive potential of these modalities, with somewhat variable QST protocols employed. Given that the application of QSTs is somewhat time consuming and requires access to standardized equipment and specially trained personnel,[79] future development of practical bedside tests is needed to offer a more practical application of QST to CPSP prediction,[80] and to determine whether these tests add predictive power independent of other measured risk factors.

Risk Factors for Other CPSP-Related Outcomes

Risk Factors for Pain Interference From CPSP

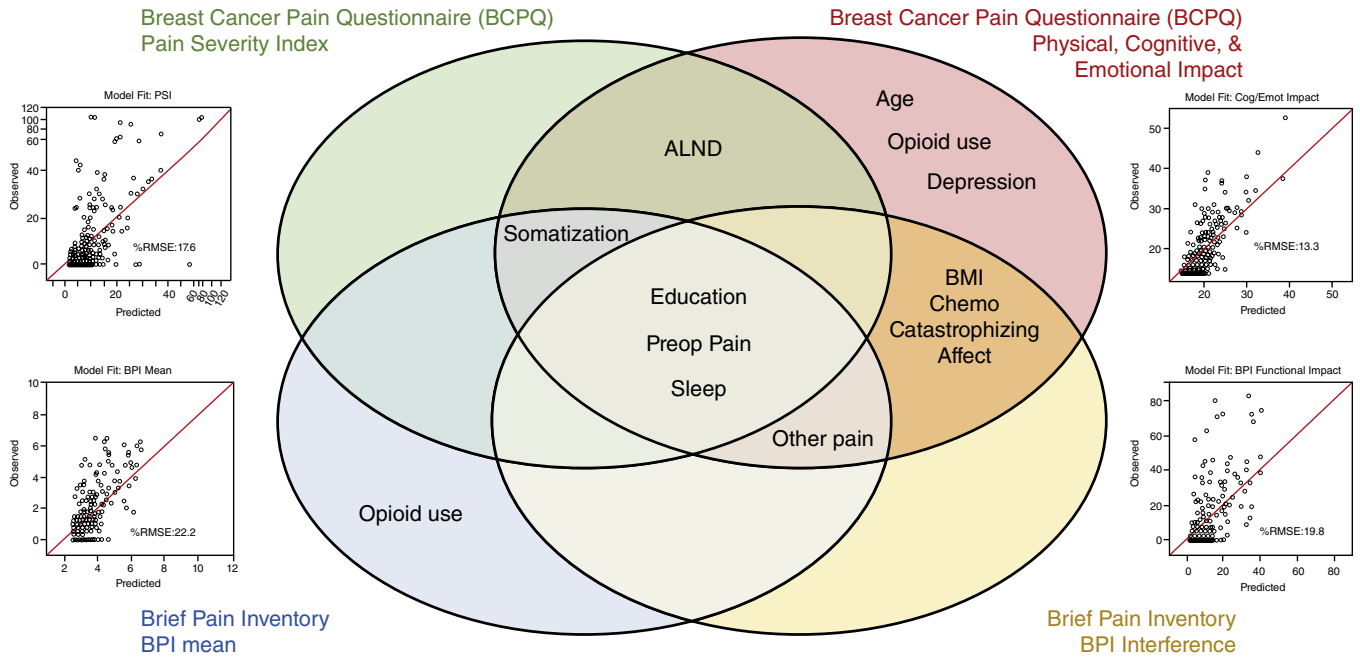
As pain is a multidimensional experience, measures of pain severity alone are insufficient to estimate the impact of pain,[81] especially when pain persists. Greater pain interference after surgery (a subscale of the Brief Pain Inventory) is closely associated with greater reported CPSP severity and the presence of neuropathic characteristics at 6 and 12 months.[14] Preoperatively assessed characteristics including state anxiety, preoperative pain status, and moderate to severe acute postoperative pain predicted greater CPSP interference.[54] A prospective longitudinal examination of a comprehensive set of preoperative variables (demographic, biomedical, and psychosocial factors) allowed an assessment of these variables' independent predictive potential for CPSP, including both pain measures of severity and impact on physical, cognitive, and emotional functioning impact.[18] Interestingly, predictors of severity and predictors of impact were only partially overlapping and depended on whether a surgery-specific questionnaire or a more general pain questionnaire was used (Fig. 24.5). Consistent independent predictors across pain outcomes included preoperative surgical area pain, less formal education, and greater baseline sleep disturbance, while pain catastrophizing, affect, younger age, higher body mass index, and chemotherapy were more consistently predictive of pain impact, but not severity.

Risk Factors for Persistent Postoperative Opioid Use

Rates of new persistent opioid use, defined as use for over 90 days after surgery in opioid-naïve patients, were 5.9% for minor surgeries and 6.5% for major surgeries (non-operative control arm 0.4%) according to a large study of 36,177 patients undergoing various procedures in the United States.[82,83] As the prevalence was similar between minor and major surgeries (OR 1.04 [0.93,1.18]), these findings suggest that prolonged opioid use after surgery cannot be simply explained by the extent of surgical injury. The multivariable analysis revealed that significant risk factors for persistent opioid use included tobacco use, alcohol and substance abuse disorders, mood disorder, anxiety, and preoperative chronic pain, thus including many of the same risk factors associated with CPSP.

Risk Factors for Neuropathic Features Involved in CPSP

Neuropathic features, such as burning, pins and needles, and stabbing, are often coincident with CPSP, with a reported range from 6% to 80%.[12,15] These features are also often associated with a



• **Figure 24.5** Assessment of comprehensive set of biopsychosocial risk factors for independent association with different post-surgical pain outcomes at one year. Schreiber KL, Zinboonyahgoon N, Flowers KM. Prediction of Persistent Pain Severity and Impact 12 months after Breast Surgery using Comprehensive Preoperative Assessment of Biopsychosocial Pain Modulators. *Ann Surg Oncol* 28, 5015–5038 (2021). https://doi.org/10.1245/s10434-020-09479-2[18]

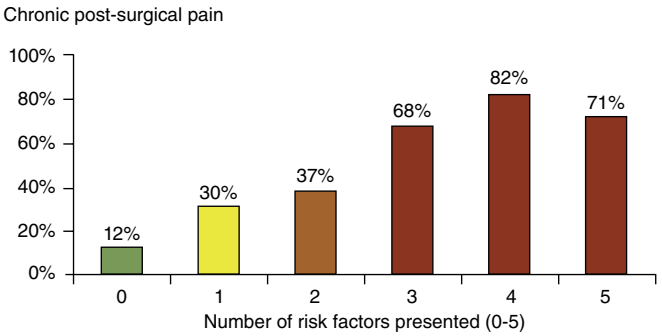
more pronounced functional impairment.[14] Similar to the close relationship between acute and chronic pain severity, early neuropathic features (on postoperative day two) are strongly associated with persistent post-surgical neuropathic features at later time points (two months), OR 4.22 [2.19–8.12].[84]

Prediction Models

Previous research has uncovered many candidate risk factors through cross-sectional and prospective longitudinal studies of CPSP. Recognizing the interrelatedness of many of these candidate risk factors, several groups have worked to identify independent predictors using multivariable regression models. Such multivariable prediction modeling aims to achieve the most accurate prediction while reducing the number of predictors to a manageable set. These models may gain a better understanding of the mechanisms underlying CPSP and enrich preventive interventional CPSP trials.

A risk index for CPSP was developed by Althaus et al. in 2012,[56] which included several previous and acute pain-related variables (preoperative pain in the operative area, other preoperative pain, acute post-surgical pain) and two variables related to physical and psychological stress (answering yes to a question about capacity overload/overstrain, and answering yes to having one of the following: sleeping disorder, exhaustibility/exhaustion, frightening thoughts, dizziness, tachycardia, feeling of being misunderstood, trembling hands, or intake of sleeping/sedation pills). This risk index was used to classify patients into low risk (zero to one risk factor), moderate risk (two risk factors), and high risk of developing CPSP (three–five risk factors presented) (Fig. 24.6). In this model, when including acute pain and other preoperative pain variables in the model, other predictors such as sex and type of surgery, minimally invasive versus open, did not emerge as independent predictors from the multivariable analysis process.

In 2015, Montes et al.[16] developed a predictive model from a large prospective multicenter cohort study that enrolled 2,929 patients scheduled for various surgical procedures (vaginal hysterectomy, abdominal hysterectomy, hernia repair, and thoracotomy). The resultant multivariable model included six predictors: preoperative pain at the surgical site, preoperative pain at another body site, more extensive surgery (higher risk for thoracotomy), younger age, and overall physical and mental condition (SF-12 physical and mental score subscales) (Table 24.4). Taken together, these factors predicted the risk of developing CPSP at four months after surgery with reasonable accuracy (approximately 70%), even when the procedure type was excluded. One advantage of a model that includes only factors known before the procedure is that it may allow the clinician to develop preventive plans for high-risk individuals in the preoperative period. This model was applied for validation at additional hospital centers and reported a similar accuracy of prediction, demonstrating reasonable geographic and temporal generalizability across populations of comparable patients.[85]



• **Figure 24.6** The probability for developing chronic post-surgical pain at six months according to risk index by Althaus's model. With permission from Althaus et al.[56]

Prevention of CPSP

Considering the putative mechanisms and modulators of CPSP, many therapies aimed at modulating or preventing CPSP involve aspects of this proposed pathophysiology, targeting events in peripheral tissues, including nerves at the site of injury, as well as events at the spinal cord or above (Table 24.5). The strategies include early and aggressive pain control by analgesic and regional anesthesia, modification of the surgical approach, and psychological-behavioral adaptation.

TABLE 24.4 Comparison of Two Models to Predict the Development of Chronic Post-surgical Pain (CPSP)

Model	Althaus et al. 2011[56]	Montes et al. 2015[16]
Study design	150 patients undergoing various types of surgery	Prospective multicenter cohort, 2929 patients undergoing vaginal hysterectomy, abdominal hysterectomy, hernia repair, or thoracotomy
Factors	1. Capacity overload (+)* 2. Preoperative pain, surgical site (+) 3. Other chronic preoperative pain (+) 4. Postoperative acute pain (+) 5. Comorbid stress symptoms (+)	1. Surgical procedure (+,–) 2. Age (–) 3. SF-12 physical (–) 4. SF-12 mental (–) 5. Preoperative pain, surgical site (+) 6. Preoperative pain, other sites (+)
Risk calculation	Summation of the five risk factors and classify them into low, moderate, and high risk of developing CPSP six months after surgery.	Complex equation from six factors calculating the risk of developing CPSP four months after surgery in 73% of the patients.

(+) increased risk, (–) decreased risk, *capacity overload = answering yes to having one of the following: sleeping disorder, exhaustibility/exhaustion, frightening thoughts, dizziness, tachycardia, feeling of being misunderstood, trembling hands, or intake of sleeping/sedation pills.

TABLE 24.5 Targets to Prevent Chronic Post-surgical Pain (CPSP): Various Interventions Can Act at Several Targets Along the Pain Pathway Initiated by Surgical Injury to Prevent CPSP

Targets and Risk Factors	Intervention
Peripheral tissues, including nerves	Modification of surgical approach
Peripheral nerve activation	Regional anesthesia
Local inflammatory response and neurogenic inflammation	Regional anesthesia Anti-inflammatory (COX-2, NSAIDs, acetaminophen)
Peripheral nerve sensitization and continued ectopic firing	Regional anesthesia Ca_v α2-δ ligands (gabapentin, pregabalin)
Changes in gene expression at dorsal root ganglion	Regional anesthesia Corticosteroids (dexamethasone) Anti-inflammatory (COX-2, NSAIDs)
Central sensitization	Regional anesthesia NMDA antagonists (ketamine, magnesium, dextromethorphan, amantadine) Corticosteroids α-2 adrenergic agonists (clonidine, dexmedetomidine) Opioid receptor agonists
Descending facilitation from the brainstem	Anti-inflammatory (COX-2, NSAIDs, acetaminophen) Anti-depressant
Limbic system and hypothalamus	Psychological-behavioral interventions Anti-depressants Anxiolytics
Cortical pain processing	Assessment and pre-screening Psychological-behavioral interventions Setting appropriate expectations
Genomic DNA leading to a predisposition to chronic pain	Assessment and pre-screening

COX-2, Cyclooxygenase-2; NMDA, *N*-methyl-D-aspartate; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

Chen Y-YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic post-surgical pain: a narrative review. *Anaesthesia*. 2021;76(1):8–17.

Analgesics and Regional Anesthesia

As the severity of acute pain after surgery is strongly associated with CPSP, excellent perioperative pain control is a logical goal. Early and proactive perioperative pain management using a combination of different analgesic agents and techniques (multimodal analgesia) has been applied to this goal, with varying effects and conclusiveness.

Analgesics

Systemic Lidocaine

Lidocaine is classically known to block voltage-gated sodium channels when administered in direct proximity to nerves. However, additional mechanisms of action may include modulation of hyperpolarization-activated cyclic nucleotide-gated channels, transient receptor potential ion channels, and certain G-protein-coupled receptors (GPCRs),[86,87] when administered systemically via the intravenous route. Administration of intravenous lidocaine is associated with analgesia beyond the duration of its pharmacokinetics, possibly by its impact on immune and neural targets and by reduction of central sensitization.[86]

A recent meta-analysis including six high-quality post-surgical studies using 1.5–2 intravenous lidocaine bolus over 10–15 min, then 1.5–2 mg/kg/h infusion until the end or 1–2 h after the operation,[32] found that perioperative lidocaine administration reduced the incidence of CPSP at three and six months after surgery (OR 0.29 [0.18 to 0.48]).[32] Intravenous lidocaine was also associated with a trend toward lower pain scores (Fig. 24.7). There were no reported adverse events of systemic lidocaine in these studies, although only one study reported lidocaine plasma levels.[88] The subgroup analysis for lidocaine infusion in a meta-analysis by Weinstein[31] also showed a preventive effect for CPSP after breast cancer surgery (Table 24.6).

Ketamine

As NMDA receptors play a pivotal role in central sensitization,[89,90] the NMDA receptor antagonist ketamine has been frequently studied for its utility in the prevention of CPSP.[26,91,92] A meta-analysis by Chapparo showed that perioperative infusion of ketamine decreased the incidence of CPSP (any value greater than 0/10) at six months, compared to a placebo (OR 0.50, [0.33, 0.76]), and the number needed to treat to prevent one patient from moderate to severe CPSP was 10.83 [5.7–109].[26]

The analysis did not show a preventive effect of ketamine at three months and was underpowered to determine a preventive effect at 12 months because of heterogeneity. Subsequent meta-analyses by McNicol et al.[92] and Klatt et al.[91] were not supportive of a long-term preventive effect for ketamine, again possibly because of heterogeneity in study design and definition of CPSP (Table 24.6), as most of the trials included were small, the populations heterogenous, and ketamine used in varying protocols (intravenous bolus 0.2–1 mg/kg or infusion 0.05–0.25 mg/kg/h).[92] An important consideration for studying the prevention of clinically meaningful CPSP (pain of at least 3/10 or higher) is that the majority of subjects entering the study do not develop the

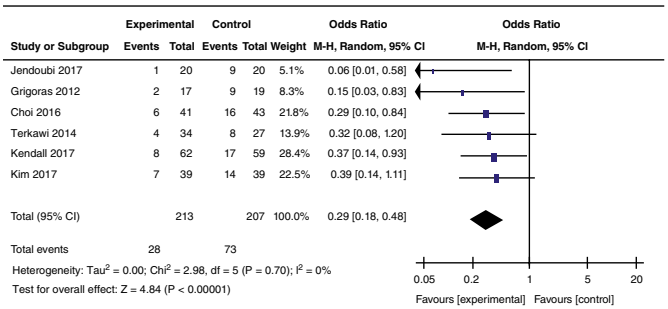


Figure 2. Effect of perioperative lidocaine infusions on CPSP in all surgery types, CPSP, chronic postsurgical pain.

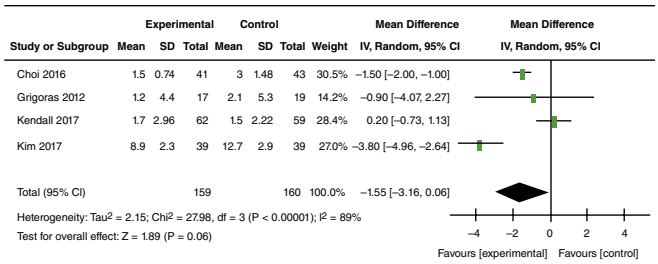


Figure 3. Effect of perioperative lidocaine infusions on pain intensity using the total score derived from the short-form McGill Pain Questionnaire.

• **Figure 24.7** Effect of lidocaine infusion on incidence (left) and intensity (right) of chronic post-surgical pain. With permission from Bailey et al.[32]

TABLE 24.6 Meta-analyses of Pharmacologic Agents to Prevent Chronic Post-surgical Pain

Medication	Surgery	Odds Ratio (95% Confidence Interval)	Heterogeneity	N	Pain Score and Follow-up (Months)	References
Lidocaine	Breast	0.24 [0.08–0.69]	I2 = 0%	97	Any pain, three to six months	Weinstein 2018[31]
	Breast, thyroid, kidney	0.29 [0.18–0.48]	I2 = 0%	420	Three to six months	Bailey 2018[32]
Ketamine	Amputation, breast, thoracic, orthopedics, abdomen/pelvis	0.50 [0.33–0.76]	I2 = 0%	516	Any pain, six months	Chapparo 2013[26]
	Amputation, breast, thoracic, orthopedics, hemorrhoid, mixed	0.84 [0.70–1.01]	I2 = 15%	771	Any pain, three to six months	McNicol 2014[92]
Gabapentin	breast, thyroid, cardiac, cesarean section, gyn, orthopedics, abdomen	0.52 [0.07–0.98]	I2 = 30.5%	356	Three to six months	Clarke 2012[94]
	Amputation, breast, thoracic, cardiac, cesarean section	0.97 [0.59–1.59]	I2 = 0%	280	Any pain, three months	Chapparo 2013[26]
Pregabalin	Cardiac, orthopedics	0.09 [0.02–0.79]	I2 = 0%	285	Three to six months	Clarke 2012[94]
	Orthopedics, cardiac, spine, thyroid	0.60 [0.39–0.93]	I2 = 28.5%	439	Any pain, three months	Chapparo 2013[26]
	Orthopedics, cardiac, spine, thyroid, thoracic, abdomen	0.87 [0.66–1.14]	I2 = 43%	1,884	Any pain, three months	Martinez 2017[95]

outcome (if only 35% develop CPSP); thus many studies are underpowered. Studies employing screening to enrich preventive trials with patients at higher risk of CPSP are needed to confirm the efficacy of ketamine in preventing CPSP. Meanwhile, ketamine is also increasingly being used to treat already established chronic pain,[89] including CPSP, although little is known about the efficacy and duration of the effect of such treatments.

Other NMDA receptor antagonists, including dextromethorphan, magnesium, memantine, and nitrous oxide, have shown some benefit in acute postoperative pain, but their role in CPSP is largely unknown.[26,79] A small randomized controlled trial showed that women treated with memantine had a modest reduction in pain (p = 0.017) and reduced referral for postoperative neuropathic pain treatment (p = 0.040) three months after mastectomy.[93]

Gabapentinoids

Gabapentinoids, including gabapentin and pregabalin, reduce pain by inhibiting the α2δ subunit of presynaptic voltage-gated calcium channels, which are upregulated after injury, forming a rational target for prevention.[79] However, the clinical evidence for their potential to prevent CPSP is still mixed.[26,94–96]

Gabapentin

Most clinical trials failed to demonstrate a reduction in the incidence of CPSP with gabapentin at three and six months. Although a meta-analysis by Clarke et al.[94] (pooled data from eight studies) showed marginal benefit over placebo (OR 0.52 [0.27–0.98]), subsequent meta-analyses by Chaparro et al.[26] (ten trials) and Verret et al.[96] (27 trials for gabapentinoids, risk ratio, 0.89 [0.74–1.07])

did not support its preventive effect. Some studies with relatively high doses of gabapentin (1,200–1,800 mg/day) have suggested an analgesic effect, but these doses are associated with significant side effects such as sedation, dizziness, and visual trouble.[79]

Pregabalin

The evidence for the preventive effect of pregabalin was also mixed. The early meta-analysis by Chapparo (five trials) and Clarke (three trials) appeared promising,[26,94] with OR 0.60 [0.39–0.93] and OR 0.09 [0.02–0.79], respectively. However, several negative unpublished trials were not included, and subsequent additional negative studies contributed further evidence against a preventive effect.[95,96] This included a meta-analysis of 18 trials in which pregabalin failed to demonstrate effectiveness in preventing CPSP (Table 24.6).[95] Similar to gabapentin, pregabalin was also associated with significant sedation and decreased satisfaction.[79]

Other Pharmacologic Agents

Peripheral and central sensitization involves the activation of inflammatory mediators and changes in the plasticity of multiple receptors along the pain pathway, with many corresponding potential pharmacologic targets aimed at preventing CPSP.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The inflammatory state from surgery leads to upregulation of several mediators, including cyclooxygenase-2 (COX-2) and prostaglandins, which can drive both peripheral and central sensitization.[97] COX inhibitors and classical NSAIDs help reduce the intensity of acute pain but still lack high quality clinical evidence showing as preventive for CPSP.[79,98]

α-2 Adrenergic Agonists

The activation of α-2 adrenoceptors spinally results in analgesia and may show important synergism with spinal opioids. However, antagonism of these receptors outside of the spinal cord results in side effects, including sedation and reduction of sympathetic tone.[99] The most commonly studied α-2 adrenoceptor agonists are clonidine and dexmedetomidine. One study showed that dexmedetomidine infusions during breast surgery reduced chronic pain intensity three months postoperatively.[100] A few studies investigating systemic or neuraxial clonidine reported efficacy in preventing CPSP. However, these studies were small, preliminary, uncontrolled, and did not have CPSP as a primary outcome.[79] Despite the potential of α-2 agonists for acute postoperative pain,[101] evidence is currently too limited to draw a conclusion regarding the preventive effect of CPSP.

Based on available data, there is very limited evidence on the preventive effects of CPSP available for other drugs, including mexiletine, acetaminophen, corticosteroids, and opioids.[79,98] High-quality, well-controlled, enriched, and stratified studies are needed to confirm or refute the efficacy of these agents.

Regional Anesthesia

Regional anesthesia (RA), including both peripheral nerve or neuraxial blocks, aims to inhibit nociceptive impulse transmission. Because RA reduces pain signals transmitted to the spinal cord and supraspinal and cortical nociceptive centers, it may also indirectly prevent glial cell activation and minimize the synaptic plasticity of neurons, thus decreasing central nervous system sensitization. Reduction of central sensitization with RA has been demonstrated in several animal models in the acute phase.[13] Local anesthetics may also have anti-inflammatory properties, which could also decrease sensitization. Animal models and in vitro studies have suggested that local anesthetics may reduce ectopic firing of neurons, expression of cytokines and other inflammatory mediators, and decrease neutrophil priming.[13,30] When used in combination with other multimodal analgesics, RA serves as a potent tool that affects many targets along the pain pathway, as shown in Table 24.5.

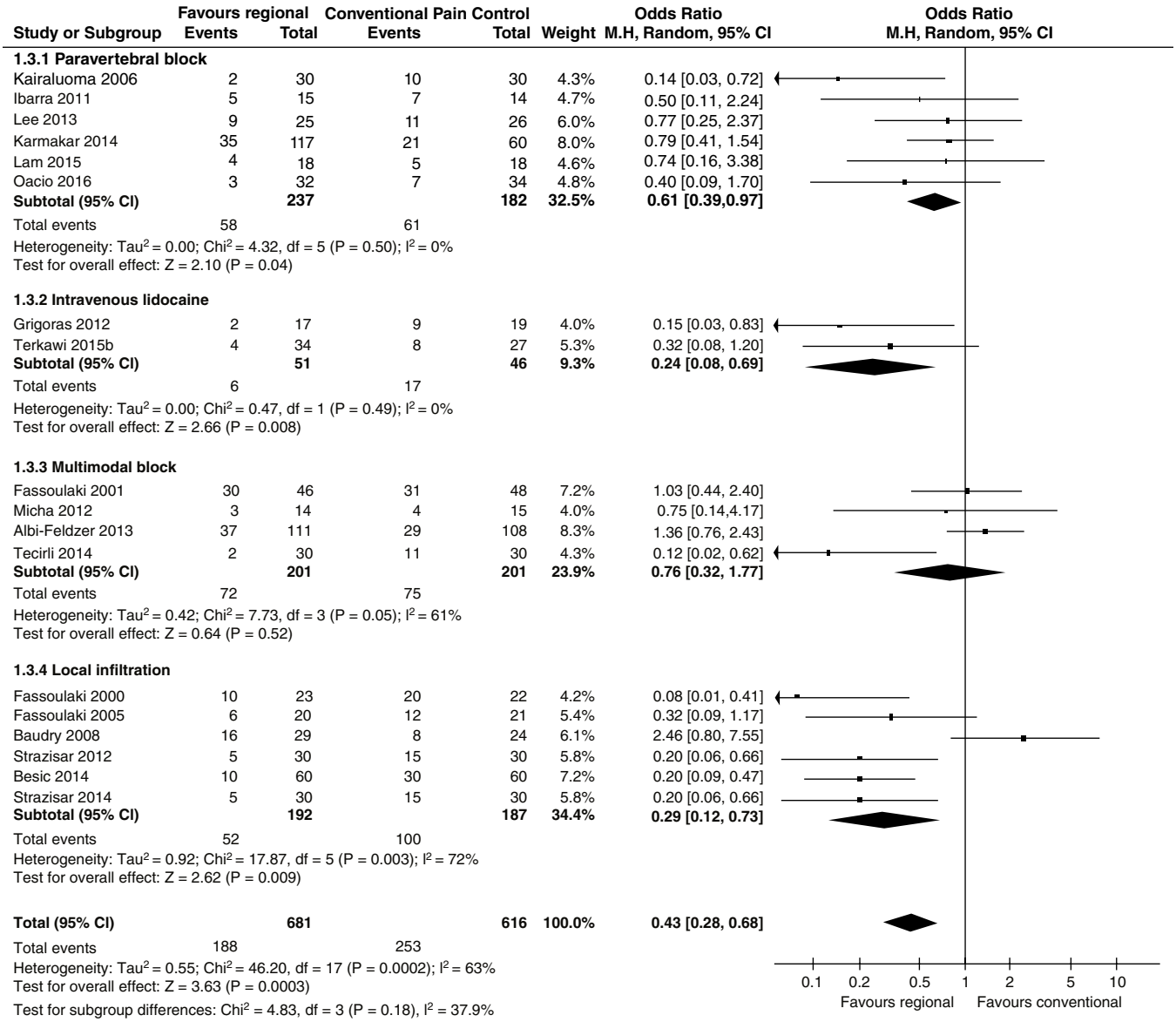
Beyond the theoretical and pre-clinical benefits, growing clinical evidence of the potential preventive impact of RA on CPSP is especially clear for breast and thoracic surgery. A meta-analysis by Weinstein et al.[31] showed that a variety of regional anesthetic techniques, including epidural block, peripheral nerve block, and local infiltration, are associated with a lower risk of CPSP (Fig. 24.8). Subgroup analysis also showed independent preventive effects for breast surgery, thoracic surgery, and cesarean delivery (Table 24.7).

Breast surgery has been the most widely studied surgical intervention for the impact of RA on CPSP. A meta-analysis[31] showed an overall benefit for CPSP from local anesthetics in multiple modes of administration, including intravenous lidocaine, local infiltration, paravertebral block, and multimodal block (intercostal block, intercostobrachial nerve block) despite the high degree of heterogeneity (OR 0.43[0.28–0.68], p = 0.0003) (Table 24.7). Subgroup analyses also showed a preventive effect for paravertebral blocks and some promise of less common alternative approaches, including intercostal and pectoral nerve-2 (PECS 2) blocks.[102,103]

A preventive effect of RA for post-thoracotomy persistent pain has been shown in a meta-analysis that favor regional anesthesia (epidural analgesia, five studies; intercostal nerve block and wound irrigation, one study each) with an OR of 0.52 [0.32–0.84] (p = 0.008).[31] Epidural block showed the greatest preventive effect for CPSP, while other modalities, including continuous wound irrigation and intercostal nerve blocks, were less effective (Table 24.7).[104,105] Nevertheless, this analysis did not include paravertebral blocks. Paravertebral blocks have been shown to provide efficacy equivalent to epidural blocks for the management of thoracic surgical pain, and paravertebral blocks may also reduce the incidence and/or intensity of CPSP.[105–107]

Overall, a reduction in CPSP after cesarean delivery is associated with RA use (transverse abdominis plane [TAP] blocks, intraperitoneal installation, or local infiltration) (OR 0.46 [0.28–0.78], p = 0.004) (Table 24.7).[31] However, the number needed to treat to prevent one case of CPSP is much higher than mastectomy or thoracotomy (19 versus 7 and 7, respectively), mainly because of the lower incidence of CPSP after cesarean delivery. The role of RA in other surgical procedures, including limb amputation, cardiac surgery, laparotomy, hernia repair, prostatectomy, and hysterectomy, is informed by a smaller pool of randomized controlled studies available for review, supporting CPSP prevention by RA for these operations is less clear.

A growing body of evidence regarding pharmacologic and interventional measures, such as RA, to prevent CPSP is welcome. However, while evidence is needed to inform clinical practice, the heterogeneity of design, definition, and methods makes the cogent interpretation of this evidence challenging. As the definition of CPSP is not universal (pain intensity and time after surgery), the estimated incidence in each study can vary considerably, from to 70%–80% in some studies, with more conservative estimates in the 20%–30% range. Although the performance of meta-analyses may abrogate this problem to some extent, the heterogeneity of studies in the pool often makes the results inconclusive.



• **Figure 24.8** Forest plot and subgroup analysis of the effect of local anesthetics and regional anesthesia on postmastectomy pain at three to 12 months. With permission from Weinstein et al.[31]

TABLE 24.7 The Effect of Regional Anesthesia on Prevention of Chronic Post-surgical Pain in Mastectomy, Thoracotomy, and Cesarean Delivery

Surgery	Regional Anesthetic Technique	Odds Ratio (95% Confidence Interval)	NNT (95% Confidence Interval)	Heterogeneity	*N*	Follow-Up (Month)
Mastectomy	Paravertebral, nerve block, local infiltrate, intravenous lidocaine	0.43 (0.28–0.68)	7 (6–13)	I2 = 72%	1297	Three to 12 months
	Paravertebral	0.61 (0.39–0.97)	NA	I2 = 0%	419	Three to 12 months
Thoracotomy	Epidural analgesia, intercostal block, wound irrigation	0.52 (0.32–0.84)	7 (4–23)	I2 = 14%	499	Three to 18 months
Cesarean section	TAP block*, intraperitoneal installation or local infiltration	0.46 (0.28–0.78)	19 (14–49)	I2 = 0%	551	Three to eight months

TAP block, Transversus abdominis plane block.
With permission from Weinstein et al.[31]

As surgical techniques and instrumentation have improved over time, the degree of surgical extent may be quite different between studies over time (e.g. reduction in the performance of radical or even radical mastectomy in the case of breast cancer, although all surgeries were grouped together as breast surgery).

Surgical Technique Modification

Surgical factors, including a greater degree of tissue or nerve injury, have been variably associated with increased incidence and severity of CPSP. Some evidence suggests that more minimally invasive surgical approaches may result in lower CPSP incidence, such as vaginal vs. abdominal hysterectomy, which is associated with a lower incidence of CPSP at all time points (Fig. 24.1).[16] Laparoscopic inguinal hernia repair is associated with less acute and chronic post-surgical pain than open inguinal hernia repair.[46–48] In breast cancer surgery, axillary lymph node dissection (ALND) is a consistent risk factor for CPSP across many studies and meta-analyses (compared to sentinel node biopsy or no axillary procedure).[18,108] Injury of the intercostobrachial nerve (ICBN) has been cited as a likely mechanism of CPSP after ALND because the ICBN traverses the axillary lymph node bed. Studies showing preservation of the ICBN during ALND are associated with a reduced incidence[109] and severity[110] of CPSP, and less sensory deficit, without a significant increase in total surgery time.[111]

In other cases, the surgical extent appears to play a less important role. Patients who undergo breast-conserving surgery (lumpectomy) do not have lower rates of CPSP than patients undergoing total mastectomy, especially when measured at later time points (> one year).[10] Less invasive surgery has also not consistently resulted in a lower incidence of CPSP in the case of thoracic surgery, especially at later time points. Compared to open thoracotomy, video-assisted thoracoscopic surgery is variably associated with a lower incidence of CPSP at six months,[112,113] but similar incidence at one year.[113] Laparoscopic cholecystectomy also tends toward reduced rates of moderate to severe CPSP, but overall laparoscopic and minimally invasive procedures versus open for cholecystectomy are associated with similar incidences of CPSP, with a similar result for colectomy.[14] These modest effects of surgical modification underline the importance of considering other risk factors in the biopsychosocial model to understand and prevent CPSP.

Psychological Intervention

Many psychological factors such as anxiety, depression, and pain catastrophizing are associated with a higher risk of CPSP. Psychological treatments such as cognitive-behavior therapy or acceptance and commitment therapy are associated with improved pain related outcomes in patients with chronic pain.[34,114–117] Increasingly, these strategies are employed as a possible preventive measure in the perioperative period, with some studies indicating that preoperative psychological interventions, such as brief acceptance-based psychological intervention,[118] along with the routine pre-surgical protocol or pain education,[119] can improve pain related outcomes, analgesic demand, anxiety,[118] and pain intensity,[119] in the acute postoperative period. However, the effect of these behavioral interventions on the prevention of CPSP remains largely unknown.

Understanding an individual patient's psychological profile may facilitate the rational application of behaviorally based preventive strategies. One study that stratified the results of a regional anesthetic based on whether patients scored higher or lower on a measure of pain catastrophizing suggested that RA (paravertebral block) provided analgesic benefit for mastectomy patients was more pronounced among patients with higher baseline catastrophizing scores.[120] More research on the differential effect of traditional or non-traditional preventive interventions for CPSP among patients with different risk factors is needed to tailor treatment according to individual risk.

Future Directions

CPSP is an active area of study, with much left to be understood, from understanding the underlying mechanisms to identifying the best preventive strategies. Having a consistent taxonomy, definition, and diagnostic criteria for CPSP is an important first step to better delineate its true incidence, temporal characteristics, and impact. Although evidence consistently shows a strong association between acute post-surgical pain and CPSP, and this risk factor dominates many of the prediction models developed up to this point, it is unclear whether acute pain should be considered a temporal correlate of chronic pain or a truly modifiable risk factor. Providing excellent control of acute postoperative pain is unquestionably an important goal in its own right, and thus proving causality may be challenging. Viewing CPSP through the lens of the biopsychosocial model, it seems clear that CPSP, like many types of chronic pain, is a complex reaction to the physical injury of surgery, which is influenced by biologic, psychological, social, and psychosocial factors. Comprehensive assessment of a wide range of putative factors from this biopsychosocial model, including pain sensitivity and psychological and genetic factors, may allow greater fidelity of risk assessment and specific preventive, personalized preventive strategies based on an individual's profile.[121] Long-term pain outcomes other than severity, including functional impairment and impact, and long term opioid use, should also be included in efficacy studies. Testing novel preventive measures, including psychological interventions, new pharmacologic agents, or combinations of multimodal analgesia, will continue to advance the capacity to prevent CPSP. Preoperative evaluation and consultation will continue to be essential to the design of preventive trials and clinical care planning.[122]

Summary

CPSP has a high impact on a patient's quality of life and is a common untoward consequence after surgery. CPSP is defined as pain developing or increasing in intensity after a surgical procedure and persisting beyond three months. Proposed mechanisms include nerve injury, peripheral and central neuroplasticity, and possibly OIH. As the type of operation and degree of tissue injury cannot solely explain the risk of CPSP, additional risk factors from the biopsychosocial model, including preexisting pain and pain sensitivity, as well as contributing psychosocial factors, may allow for a more comprehensive explanation and prediction of CPSP. Clinical evidence regarding the efficacy of preventive measures has been mixed, but mainly positive for systemic lidocaine, ketamine, RA, and surgical technique modification for certain procedures. Although our understanding of CPSP has grown tremendously over the years, more studies are needed to understand this complex phenomenon.

Key Points

- CPSP is a relatively common consequence of surgery and may negatively impact patients' quality of life. Effective prevention of CPSP is an important clinical goal, as informed by a growing body of studies.
- CPSP is defined as chronic pain that develops or increases in severity after a surgical procedure, which persists beyond the healing process, typically at least three months or longer. CPSP is most commonly localized to the surgical field, but may also include pain within the innervation territory of a nerve affected by the surgery. Other causes must be excluded from the diagnosis of CPSP to be made.
- The mechanism by which CPSP develops is not completely understood, but it likely includes nerve injury and neuroplasticity and may involve OIH. Preventive analgesia, opioid-sparing strategies, and modification of surgical techniques may modify the transmission of the nociceptive signal and subsequent maladaptive plasticity in the peripheral and central nervous systems.
- Risk factors for CPSP may be categorized using the biopsychosocial model, ranging from biologic factors such as surgical extent, genetics, age, sex, preexisting pain, and pain modulation, to psychological and social factors such as anxiety, depression, catastrophizing, coping strategies, and community support and resources. Recognizing and measuring these baseline factors may inform the assessment of CPSP risk. Some general and procedure-specific predictive models using some of these risk factors have been proposed to help stratify risk and tailor preventive measures.
- Preventive measures may include minimally invasive surgery, aggressive acute postoperative pain control, and preventive analgesia. Several perioperative pharmacologic interventions such as ketamine, lidocaine infusion, and RA appear promising for the prevention of CPSP, although the evidence remains somewhat mixed.
- Successful preventive treatment for CPSP likely depends on identifying the type of pain, recognizing the type of individual, and employing a multimodal, multi-disciplinary, and personalized approach to tailor treatments according to individual risk factors.

Suggested Readings

Haroutiunian S, Nikolajsen L, Finnerup N, Jensen T. Neuropathic component in persistent postsurgical pain: A systematic literature review *Pain.* 2013;154(1):95–102.

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Evaluation and Pharmacologic Treatment of Postoperative Pain

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Pain after a surgical procedure is inevitable. However, as stated by Haruki Murakami, "Suffering is optional."

Management of postoperative pain has come a full circle. The Joint Commission recognized the underassessment and undertreatment of pain in 2000 and introduced the concept of pain as the fifth vital sign.[1] However, the emphasis of The Joint Commission on the use of opioids for pain control has been criticized as a contributing factor in the prescription opioid epidemic that the modern world is facing.[2] Enhanced recovery pathways involving multimodal analgesia with emphasis on limiting opioids have become the cornerstone of managing pain in the postoperative setting.

A majority of patients who undergo surgery report inadequate pain control.[3] Causes of ineffective pain control include lack of accurate assessment and patient factors such as fear of adverse effects or addiction from medications.[4] Poorly controlled pain increases the incidence of postoperative complications such as pneumonia, delirium, delayed wound healing, and evolution of acute pain into chronic pain,[5,6] while optimal pain control improves patient satisfaction and enhances the quality of recovery.[4,7]

Pain management is an important ethical responsibility of every clinician. Adequate pain control requires finesse to find the delicate balance between minimizing immediate adverse effects and preventing long term dependence on opioids. Many institutions have developed standardized guidelines for perioperative analgesia in the form of enhanced recovery after surgery (ERAS) protocols. The acute pain service is an integral part of most anesthesiology departments, with a focus on providing optimal pain management in the postoperative period. Assessment and management of pain in opioid dependent patients and pain in children are beyond the scope of this chapter and are discussed in Chapters 27 and 28, respectively.

Management of postoperative pain starts with an accurate assessment. Guidelines from the American Pain Society recommend that "*clinicians use a validated pain assessment tool to track responses to postoperative pain treatments and adjust treatment plans accordingly*."[3] Effective pain management takes into account the surgical procedure performed and individual patient factors such as comorbidities and the use of preoperative narcotics.[3] The goal of pain assessment is to determine the analgesic requirements of the patient and if there is a need to change the treatment plan.[3]

Evaluation of pain can be extremely challenging as pain is largely subjective.[4,8] There are multiple evaluation tools available for postoperative pain assessment. However, most require patient participation, which can be difficult in the immediate postoperative period when the patient is still emerging out of anesthesia.

Comprehensive postoperative pain assessment includes several components. Although severity is the most easily quantifiable measure, attention should be paid to other characteristics of pain, including location, quality, onset, progression, radiation, aggravating and relieving factors, and effects of therapy.[3] Pain symptoms that are at an inappropriate site or of unexpected severity based on the surgical procedure performed should be investigated for causes other than the surgery itself.[3,4] Unexpectedly high pain can be because of opioid tolerance, anxiety, a new medical problem unrelated to surgery, or a potential complication from the surgery itself.[3]

Evaluation of Pain Using Pain Scales

Numerous self-reported pain scales have been developed to quantify the severity of pain (Table 25.1). Among the most frequently used scales are:

Visual Analog Scale (VAS)
Numeric Rating Scale (NRS)
Verbal Rating Scale (VRS)

Visual Analog Scale

VAS is measured by drawing a 10 cm or 100 mm straight line. This line is anchored at each end by a perpendicular line that represents two extremes of pain—no pain on the left end and most intense pain imaginable on the right end. The patient is asked to make a mark at a point on the line, which represents the patient's level of perceived pain intensity, and the scale is scored by measuring the distance from the end with no pain to the patient's mark.[9–12] The line may be depicted with a horizontal or vertical orientation, though a horizontal line is generally preferred.[10] The VAS has often been recommended as the measure of choice for assessment of pain intensity.[10]

It has been suggested that a single VAS score is probably not the most accurate measure of a patient's pain but is probably within the range of +/–20 mm.[13] A change of 10 mm out of 100 mm pain VAS is considered the minimal clinically important difference, i.e. the minimal change in a pain VAS score that would indicate a significant change in a patient's pain intensity, and the VAS of 33 or less signifies acceptable pain control after surgery.[14,15] VAS is sensitive to treatment effects[10] and shows ratio level scoring properties.[10,16] The reliability of VAS depends on the patient's

TABLE 25.1 Commonly Used Scales for Postoperative Assessment of Pain

Pain Scale	Range	Advantage	Disadvantage
Visual Analog Scale	0–10 (cm) 0–100 (mm)	Sensitive to treatment effect Shows ratio level scoring property	Requires visual motor coordination from the patient
Numeric Rating Scale	0–5(6) 0–10(11) 0–20(21) 0–100(101)	Verbally scored Easy to administer High compliance Sensitive to treatment effect	Lacks ratio level scoring property
Verbal Rating Scale	No pain to most intense pain	Easy to understand Better compliance in elderly	Requires patient familiarity with adjectives Interval between adjectives not equal

ability to place a mark at the intended spot and requires visual and motor coordination.[11] VAS may be challenging to obtain in patients with cognitive impairment,[10] and freedom of choice provided by VAS could be confusing for some patients.[12]

VAS shows a good correlation with NRS in patients with arthritis.[12] However, its usefulness may be limited in the immediate postoperative period, especially in phase 1 of recovery when the patient may have residual effects of anesthesia, blurred vision, or nausea.[13] Nonetheless, it is a simple, useful, and valid tool to assess and reassess a patient's pain and response to therapy if the problems intrinsic to the score itself are considered.[13]

Numerical Rating Scale

NRS consists of a numeric scale ranging from 0 to 10, 0 to 20, or 0 to 100.[3,9,10,17,18] Zero represents no pain, whereas the higher end (10, 20, or 100) represents the most intense pain. NRS can be administered verbally or in a written format.[10,17] When presented graphically, the numbers are often enclosed in boxes, and the scale is referred to as an 11 or 21-point box scale depending on the number of levels of discrimination offered to the patient.[17] Its advantages include that it is simple, easily understood by the patient, and is easily administered and scored by the caregiver.[10] It is a valid tool with a high compliance rate and good consistency over time, which correlates positively with other measures of pain and shows sensitivity to treatments.[8,10] The principal limitation of NRS is that it does not have ratio qualities, implying that the difference between two and four and the difference between four and six may not represent equivalent intervals in terms of scaling of the intensity of pain.[10] Its major advantage over VAS is that it can be used in patients with visual impairment by recording verbal responses.[17] One author has described the successful use of a six-point NRS (0-5) during the postoperative period in patients with dementia.[17] The six-point NRS is a simplified version of NRS 11.[17] It was reported to be reliable, valid, and much easier to administer in patients with dementia.[17]

The 100 mm VAS and NRS 11 are the most commonly used scales for postoperative pain assessment.[14] A limitation of both scores is that the definition of worst imaginable pain differs among individuals.[10] This can be taken care of by providing the patient with some context of the worst imaginable pain.

Verbal Rating Scale

The VRS comprises a list of adjectives that describe increasing levels of pain.[9,18] The most common words used are no pain, mild pain, moderate pain, and severe or intense pain.[18] To simplify the documentation, each adjective is assigned a number. The least intensity (no pain) is assigned the number 0, with subsequent intensity assigned one number higher.[9,18] The strengths of VRS include its simplicity, ease of administration, and scoring.[10] It is straightforward for patients to comprehend, which is important in the very early postoperative period and is most easily understood by patients with cognitive impairment.[19,20] VRS has much superior compliance rates in the elderly than other scales.[10] One of the pitfalls of this scale is that the interval between each adjective is not equal.[18] Also, the patient must be familiar with words used to describe the pain and should be able to choose the one that describes his/her pain accurately.[10]

Clinical Evaluation of Pain

Along with self-reporting of pain, patients should be observed for clinical signs of distress that include:[8]

- facial expression of pain, such as grimacing;
- audible expression of pain, such as moaning or crying;
- ambulation in the form of limping or posture, e.g. lying in a fetal position; and
- avoidance of activities or specific movements.

Assessment tools such as the behavioral pain scale (BPS) and critical-care pain observation tool (CPOT) can help clinicians assess pain control in patients with cognitive impairment or sedation.[3,21] The CPOT has four components[22,23]—facial expression, body movements, resistance to passive flexion, and compliance to the ventilator in intubated patients or vocalization in extubated patients. The scale is scored from zero to eight, with zero being no pain and eight being maximum possible pain (Table 25.2).[23] The BPS has three components—facial expression, upper limb movements, and compliance with mechanical ventilation, scored on a scale of one to four.[23–25] BPS scores range from three (no pain) to 12 (maximum pain) (Table 25.3).[23]

Both scales are used routinely in the intensive care unit to assess pain in intubated and sedated patients. Increases in heart rate and blood pressure have been suggested as sympathetic responses to noxious stimuli. However, caution must be used when interpreting changes in these vital signs that may also be influenced by other factors, such as postoperative use of vasopressors and inotropes. Behavioral and physiologic indicators are especially important indices for the assessment of pain in patients who are unable to self-report.[22]

Functional Assessment of Pain

Another objective way to access pain is to ascertain the extent to which pain interferes with functional ability after surgery.[4] It may vary with the type of surgery performed. Some examples include taking a deep breath and performing incentive spirometry after abdominal surgery, participating in physical therapy after musculoskeletal or spine surgery, or swallowing after tonsillectomy.[3,4] NRS 11 can be used to assess the impact of pain on functional ability with similar anchors as pain (0= does not interfere, 10= completely interfere).[8] However, objective measures should not be used as the sole criterion for assessing pain in patients who can participate in assessment as there is marked interindividual variability in pain behaviors at a similar level of pain.[3]

TABLE 25.2 Critical-Care Pain Observation Tool (CPOT)[23]

Component	Description	Score
Facial expression	No muscular tension observed	Relaxed 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense 1
	All of the above facial movements plus eyelid tightly closed	Grimacing 2
Body movements	Does not move at all	Absence of movements 0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection 1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness 2
Muscle tension evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed 0
	Resistance to passive movements	Tense, rigid 1
	Strong resistance to passive movements, inability to complete them	Very tense, rigid 2
Compliance with ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement 0
	Tolerating ventilator or movement	Coughing but tolerating 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator 2

Total zero to eight, with zero being no pain and eight being maximum possible pain.
Adapted from Rijkenberg S, Stilma W, Bosman RJ, van der Meer NJ, van der Voort PHJ. Pain measurement in mechanically ventilated patients after cardiac surgery: comparison of the behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT). *J Cardiothorac Vasc Anesth.* 2017;31(4):1227–1234.

TABLE 25.3 Behavioral Pain Scale (BPS)[23]

Component	Assessment	Score
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4

BPS scores range from 3 (no pain) to 12 (maximum pain).
Adapted from Rijkenberg S, Stilma W, Bosman RJ, van der Meer NJ, van der Voort PHJ. Pain measurement in mechanically ventilated patients after cardiac surgery: comparison of the behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT). *J Cardiothorac Vasc Anesth.* 2017;31(4):1227–1234.

Assessment of pain requires frequent reassessment, guided by response to therapy and the type of surgical procedure.[3] It has been suggested that the progress of pain relief of an individual patient can be evaluated better by trending pain scores on a graph instead of looking at individual numbers.[19] The effectiveness and adverse effects of analgesic medications should be evaluated at frequent intervals, and appropriate adjustments should be made to the regimen for each patient.[3] Pharmacokinetic principles such as route of administration and time to achieve peak analgesic effect should be kept in mind when evaluating the response to medications. Most oral analgesics require 1 to 2 h to reach peak effect, whereas for analgesics administered parenterally, it is 15 to 30 min.[3] An important part of the evaluation is a documented follow-up assessment to note the efficacy of the therapy and the patient's satisfaction with it.[3,4] Pain should be assessed at rest and with activity. The goal should be optimum pain control with activity, which is often more difficult to achieve.[3,19,26,27]

Pharmacologic Treatment of Pain

Pharmacologic treatment of postoperative pain has traditionally favored the use of opioids as the primary analgesic treatment. However, with the growing realization of the adverse effects of opioids, including nausea, vomiting, constipation, urinary retention, respiratory depression, sedation,[28] and risk for opioid dependence,[3] the practice is slowly changing to optimize the use of non-opioid medications first.

The ideal treatment of postoperative pain involves the use of multimodal analgesia regimens. Multimodal analgesia is defined as using multiple analgesic agents and techniques that act in a synergistic or additive manner.[3] The multimodal approach aims to target multiple different pain receptors within both the central and peripheral nervous systems to provide maximal pain relief and minimize adverse effects.[3] Multimodal analgesia is discussed in depth in Chapter 26. Many enhanced recovery (ERAS) protocols

TABLE 25.4 Systemic Opioid and Nonopioid Analgesic Options

Agent	Delivery	Analgesic Ceiling	Side Effects	Comments
Opioids	PO, IV PCA, IM	No	Induced hyperalgesia, nausea, vomiting, sedation, respiratory depression, pruritus, constipation, urinary retention	Side effects limit full their analgesic potential
Acetaminophen	PO, IV	Yes	Hepatotoxicity	Coadministration with opioids appears to provide opioid-sparing analgesia but may not reduce opioid-related side effects
NSAIDs	PO, IV, IM	Yes	Renal, GI, platelet inhibition, inhibition of bone healing, inhibition of osteogenesis, cardiovascular	Coadministration with opioids appears to provide opioid-sparing analgesia but may not reduce opioid-related side effects
COX-2 inhibitors	PO	Yes	Renal, cardiovascular, inhibition of bone healing, inhibition of osteogenesis	Coadministration with opioids appears to provide opioid-sparing analgesia but may not reduce opioid-related side effects
Ketamine (low dose)	IV	Yes	No cognitive impairments or psychotomimetic effects are seen with dosing of 0.25 mg/kg	May attenuate both postoperative pain and chronic pain; may attenuate opioid-induced hyperalgesia
Gabapentin and pregabalin	PO	Unknown	Dizziness, somnolence, ataxia, memory impairment, weight gain, edema, altered vision	May be useful for acute analgesia and chronic antihyperalgesia, pending further study

COX, Cyclooxygenase; *IM*, intramuscular; *IV*, intravenous; *NSAID*, nonsteroidal anti-inflammatory drug; *PCA*, patient-controlled analgesia; *PO*, per oral.
(printed with permission from Hanna MN et al. In: H Benzon et al. (eds) Practical management of pain, 5th edition. Philadelphia: Elsevier, 2014, pp. 271–297).

incorporated multimodal analgesia to minimize opioid use and facilitate pain control and recovery. Recently, the American Pain Society published updated guidelines for the management of postoperative pain.[3] These guidelines provide the reference for clinicians treating postoperative pain to devise a plan, individualized based on patient's expectations, comorbidities, and the surgical procedure.

Pharmacotherapy for pain can be broadly divided into opioid and non-opioid medications (Table 25.4). Non-opioid pain medications should be the first line of treatment for postoperative pain. It is a heterogeneous group of medications with a diverse mechanism of actions and includes:

- Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen
- Local anesthetic agents: lidocaine
- Ketamine
- Gabapentin, pregabalin
- Alpha two agonists

Acetaminophen and Non-steroidal Anti-inflammatory Drugs

Acetaminophen (Paracetamol) is an integral part of any multimodal analgesia regimen. It is the most commonly prescribed analgesic for the treatment of acute pain.[29]

Its mechanism of action is not precisely understood. It has been found to cross the blood-brain barrier.[30] There are several possible explanations for its mechanism, including inhibition of central prostaglandin synthesis,[29–33] inhibition of central nitric oxide generation via inhibition of *N*-methyl-D-aspartat (NMDA) e or substance P,[29,34] activation of descending serotonergic pathways, and inhibiting the uptake of endocannabinoids from the extracellular space.[29,31,35,36]

It can be administered orally, rectally, or intravenously (IV). The peak acetaminophen plasma concentration occurs 3 to 4 h after a rectal dose, 45 to 60 min after an oral dose, and 15 min after IV infusion.[37–39] IV paracetamol may be more than suitable in patients in whom faster onset is desirable and oral route is not available.[29] However, the cost of the IV formulation may be a limiting factor as well as its availability. The dosage for oral and IV acetaminophen in adults is 1 gram every 4 to 6 h, not to exceed 4 grams in a 24 h period. Once the patient can tolerate oral drugs, oral acetaminophen can be scheduled every 4–6 h to ensure therapeutic plasma levels. Acetaminophen can be administered rectally as an alternative to the oral route. However, its main disadvantage is unpredictable bioavailability.[40,41]

Acetaminophen is metabolized in the liver and excreted by the kidney. The dose interval should be at least 6 h in patients with renal insufficiency (creatinine clearance <=30 mL/min).[29,42] Hepatotoxicity is rare and occurs when supra-therapeutic doses are administered or in patients with preexisting hepatic disease.[29]

In a Cochrane meta-analysis of 75 studies, IV acetaminophen was found to be a useful adjunct to opioids as it reduces opioid consumption.[29] Acetaminophen lacks the adverse effect profile of NSAIDs, such as interference with platelet function, and is safe in patients with peptic ulcers, gastrointestinal bleeds, and asthma.[29,43]

NSAIDs are a diverse group of medications that have anti-inflammatory, antipyretic, and analgesic effects.[28] Surgical stimulus leads to the release of inflammatory mediators such as prostaglandins, leading to stimulation of nociceptors and perception of pain.[44] NSAIDs exhibit these effects by inhibiting the cyclooxygenase enzymes (COX) and, therefore, inhibit the synthesis of prostaglandins that are mediators of acute inflammatory response. Prostaglandins are important mediators of peripheral and central nervous system hyperalgesia as well.[45] COX has two

major isoforms with different functions: COX-1 and COX-2. NSAIDs are classified into two major groups based on their mechanism of action on each of these enzymes. The non-selective reversible competitive inhibitors block both COX-1 and COX-2 enzymes, whereas the selective ones only block the COX-2 isoform. The COX-1 enzyme mediates platelet aggregation, hemostasis, and gastric mucosal protection. Non-selective NSAIDs may cause adverse effects via inhibition of COX-1, including gastrointestinal bleeding, impaired renal function, inhibition of platelet aggregation, and inhibition of bone healing and osteogenesis. The pharmacokinetic profile of the drug should guide selection in the perioperative period. When given at higher doses, NSAIDs have faster onset with a longer duration.[44] Therefore in the initial postoperative period, patients should be started on a high dose, followed by titrating the dose down to limit adverse effects (Table 25.5).[44]

The development of selective COX-2 inhibitors was based on the premise that selective inhibition of COX-2 would provide analgesia without the side effects associated with COX-1 inhibition. Although selective COX-2 inhibitors are associated with a lower incidence of gastrointestinal complications,[46] and exhibit minimal platelet inhibition even when administered in supratherapeutic doses,[47] recent data indicate that COX-2 inhibitors may be associated with a higher incidence of cardiovascular events such as myocardial infarction.[48] Because COX-2 inhibitors inhibit PGI2, these agents may contribute to coronary thrombosis via the unopposed action of thromboxane A2.[49] A meta-analysis of rofecoxib trials indicated that administration of rofecoxib is associated with a 2.3-fold greater risk for cardiovascular events,[48] leading to the withdrawal of rofecoxib. Some data suggest that celecoxib is also associated with a higher incidence of cardiovascular events.[50–52] Therefore it should be avoided in patients with coronary artery disease.

Multiple studies have shown the opioid-sparing effects of NSAIDs by decreasing the opioid requirements, reducing adverse effects, and improving patient satisfaction. NSAIDs have been shown to be effective in almost all types of surgeries.[44] Several meta-analyses suggest that the use of NSAIDs, COX-2 inhibitors, or acetaminophen in combination with IV patient-controlled analgesia (PCA) results in an opioid-sparing effect. However, only non-selective NSAIDs have been shown to decrease the relative risk for some opioid-related side effects (e.g. PONV, sedation), which leads to early discharge as patients can tolerate oral fluids early.[28,53–57]

NSAIDs and acetaminophen have different mechanisms of action,[3] and it has been proven that a combination of both is superior to either drug alone.[58] The American Pain Society, in the most recent guidelines for the management of perioperative pain, recommends that all the patients should receive acetaminophen and/or NSAIDs as part of multimodal analgesia unless contraindicated.[3]

TABLE 25.5 Commonly Used NSAIDs for Postoperative Pain

Drug	Oral dose	Frequency	Maximum Dose in 24 h
Aspirin	600 mg	QID	
Naproxen	250–500 mg	BID	
Naproxen sodium	275–550 mg	BID	
Ibuprofen	200–800 mg	QID	3200 mg
Ketoprofen	50 mg–75 mg	BID-QID	300 mg
Ketorolac Limit to <five days	Oral 10 mg IV 15 mg	QID QID	40 mg 60 mg
Diclofenac	50–75 mg	BID-QID	200 mg
Etodolac	200–300 mg	BID-TID	1000 mg
Nabumetone	500–750 mg	BID	1500 mg
Meloxicam	7.5 mg	BID	15 mg
Celecoxib	100–200 mg	qD-BID	200 mg

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Local Anesthetic Agents—Intravenous Lidocaine

Local anesthetics are used for peripheral nerve blocks, neuraxial analgesia and anesthesia, local infiltration, topical use, and intravenous administration.

Lidocaine has been used as an adjunct to general anesthesia to reduce inhalational anesthetic requirements,[59] and reduce airway reactivity with extubation in patients who smoke.[60] It is commonly used at the time of induction of general anesthesia to blunt the sympathetic response with laryngoscopy. Intravenous lidocaine (IVL) has been found to be beneficial in several surgical procedures, especially abdominal surgeries. However, the effectiveness varies with the type of surgical procedure.

Intravenous lidocaine has analgesic and antihyperalgesic properties and is known to attenuate the proinflammatory effects of surgery itself.[59–61] The precise mechanism by which IVL exerts these effects remains unclear. Possible explanations include a blockade of sodium channels, which is common to all local anesthetics, along with inhibition of G protein-coupled receptors, which leads to blockade of priming of polymorphonuclear neutrophils, attenuating inflammation.[59,60,62,63] Antihyperalgesic effect of lidocaine is modulated by a decrease in the activity of neurons and NMDA receptor-mediated postsynaptic depolarization in the spinal cord.[59,64–67]

The benefits of perioperative lidocaine infusion include reductions in pain, nausea, ileus duration, opioid requirement, and length of hospital stay, promoting early rehabilitation.[60,68] Multiple studies have confirmed these effects in open and laparoscopic abdominal surgeries,[69–71] including colectomy, cholecystectomy, and appendectomy.[59,60] Typical dose includes a bolus of 1.5 mg/kg followed by infusion of 1.5-3 mg/kg/h. The clinically effective serum concentration of lidocaine for pain relief has been estimated at 2 to 10 μg/mL.[69] IVL infusion can be continued postoperatively at a dose of 0.5-1 mg/min. Maximum benefit has been observed within 24 h of surgery, with no additional benefit beyond that duration.[60,72]

In open prostatectomy, thoracic, and major spine procedures, IVL has been shown to decrease postoperative pain and opioid consumption and improve functional outcomes.[60] In breast surgery, it may help to prevent the development of chronic postsurgical pain.[60,73] However, it has shown no benefit in patients undergoing total abdominal hysterectomy, total hip arthroplasty, or renal surgery.[60] Opioid-sparing effects of IVL are particularly helpful in obese patients undergoing bariatric procedures to help mitigate the respiratory depressant effects of opioids.[60,74]

It is rare for patients to develop toxic symptoms. However, healthcare providers need to know the presenting symptoms of

toxicity, including tinnitus, perioral numbness, and cardiac dysrhythmia.[60] Monitoring plasma lidocaine levels may be considered in patients at increased risk for lidocaine toxicity, such as those with abnormal liver or kidney function or those who cannot be queried about symptoms of lidocaine toxicity.[60]

To summarize, intravenous lidocaine is inexpensive, easy to administer, relatively safe, and effective as an analgesic to reduce opioid requirements and facilitate earlier recovery in appropriately selected surgical procedures.[59]

Ketamine

Ketamine is a commonly used anesthetic agent. Recently, there has been renewed interest in the use of ketamine as an analgesic agent in subanesthetic doses.[75] Ketamine is a noncompetitive antagonist of NMDA glutamate receptors in nociceptive neurons.[76] It is most commonly used clinically as a racemic mixture, although the S (+) enantiomer is more potent than the R(-) enantiomer.[75,77,78] Ketamine is used most commonly intravenously and can be used intramuscularly. The safety of the neuraxial route has not been established and is therefore not recommended.

Typically low doses are used intraoperatively, including 0.25–0.5 mg/kg slow bolus injection intravenously before incision, dose depending on the expected pain intensity after the procedure.[75] Maintenance doses can be repeated injections of 0.125–0.25 mg/kg ketamine at 30-min time intervals or a continuous infusion of 250–500 μg/kg/h.[75] It has been recommended to decrease the dose when planned to continue postoperatively or stop the infusion at least 60 min before the end of surgery to prevent prolonged recovery for surgeries lasting more than 2 h.[75] The optimum dose in the postoperative period is uncertain.

Ketamine reduces postoperative pain, both at rest and with movement, and postoperative opioid requirements make it a suitable adjunct for analgesia, regardless of the anesthetic technique used. In a recent systematic review, perioperative intravenous ketamine reduced postoperative opioid consumption by 8 mg morphine equivalents over 24 h (95% confidence interval [CI] 6–9; 19%) and by 13 mg (95% CI 10–15; 19% from 67 mg) over 48 h when compared with a placebo in a variety of surgical procedures.[79] In a meta-analysis of 36 randomized control trials, Wang et al. found that adding ketamine to morphine/hydromorphone PCA provides a small improvement in postoperative analgesia while reducing opioid requirements.[80]

Ketamine has been shown to attenuate central sensitization and chronic postsurgical pain, reduce opioid-induced hyperalgesia (OIH) and opioid tolerance in opioid dependent patients.[79,81] OIH is a paradoxical increase in pain because of opioid administration, which does not respond to escalating opioid doses. In contrast, opioid tolerance responds to increasing the dose of opioids.[78,79] One of the proposed mechanisms in the development of OIH involves activation of NMDA receptors. Treatment of OIH involves tapering off the opioids and administration of NMDA modulators such as ketamine.[78,79] Ketamine does not cause respiratory and cardiovascular depression, which could be beneficial in patients with tenuous respiratory and cardiovascular status.[28]

The adverse effects of ketamine are dose-dependent and include hypersalivation, nausea and vomiting, and central nervous system (CNS) psychotomimetic effects, including hallucinations, nightmares, and delirium.[79] However, the adverse effects of ketamine are minimal when used at lower doses for analgesia. The CNS adverse effects can be further reduced by premedicating with benzodiazepines, especially midazolam.[82]

Gabapentin, Pregabalin

Gabapentin and pregabalin are commonly used for the treatment of neuropathic pain. Gabapentin is an inhibitor of calcium influx at voltage-dependent calcium channels, which decreases excitatory transmitter release and spinal sensitization.[83]

Gabapentin and pregabalin are available only for enteral use. Gabapentin absorption is dose-dependent.[84] Gabapentin is absorbed in the upper small intestine, whereas pregabalin is absorbed throughout the small intestine and colon. Therefore pregabalin may be preferred in patients with small bowel pathologies.

Recommendations from the American Pain Society suggest that gabapentin or pregabalin be administered preoperatively for major surgeries with a severe anticipated intensity of pain.[3] Although the optimum dose has not been described, typical doses evaluated in trials include 600 or 1200 mg of gabapentin or 150 or 300 mg of pregabalin, administered 1–2 h preoperatively.[3] There is limited evidence to show postoperative administration to be effective (typically gabapentin 600 mg as a single or in multiple doses and pregabalin 150 or 300 mg after 12 h).[3] Doses of both drugs need to be reduced in patients with altered renal function. The effect of perioperative gabapentin and pregabalin has not been consistent across studies. A recent meta-analysis found the risk of adverse events with gabapentin and pregabalin to outweigh the modest benefit of the opioid-sparing effect.[85,86] In contrast, some studies support the theory that perioperative gabapentin may reduce the incidence and intensity of postoperative pain up to six months after otolaryngology, orthopedic, mastectomy, and abdominal/pelvic operations.[83,87]

In a randomized controlled trial including 422 patients to evaluate the efficacy of perioperative gabapentin, 1200 mg was administered preoperatively plus 600 mg every 8 h continued for 72 h after surgery. The study was terminated prematurely as gabapentin did not affect the time to pain cessation, the rate of pain resolution, or the proportion of patients with chronic pain at six months or one year following surgery.[83] However, perioperative gabapentin was found to have a modest effect in promoting postoperative opioid cessation and, therefore, may have a role in preventing the development of chronic opioid use after surgery. Pregabalin has a great opioid-sparing effect in the first 24 h and significantly reduces opioid-related side effects.[88] Similar results were reported in a study of patients undergoing total knee arthroplasty.[89] The side effects of gabapentin and pregabalin are respiratory depression, sedation, and dizziness, particularly at high doses. Their role in the intra and postoperative pain relief is limited by the potential for serious respiratory depression. The Food and Drug Administration (FDA) recently issued a warning for both gabapentin and pregabalin to be used cautiously in conjunction with opioids and other CNS depressants and in elderly patients and those with chronic obstructive pulmonary disease. Their use is further limited because both these drugs can only be administered orally, which can be challenging in the immediate postoperative period.

α-2 Agonists

The α-2 adrenergic receptor agonists such as dexmedetomidine and clonidine have been used via several routes perioperatively. We will discuss the use of dexmedetomidine relevant to adult patients in this chapter as dexmedetomidine is more selective than clonidine for alpha two receptors. The use of dexmedetomidine in pediatric patients as a preoperative medication is beyond the scope of this chapter.

α-2 Agonists have sedative, analgesic, and anti-sympathetic effects.[90] Dexmedetomidine has been shown to attenuate OIH.[91]

Most commonly used regimen includes a loading dose of 0.5–1 mcg/kg over 10 min followed by an infusion of 0.3–0.7 mcg/kg/h.[91,92] In patients undergoing thoracic surgery, intraoperative dexmedetomidine improved pain scores and had an opioid-sparing effect.[92] Opioid-sparing effect was also observed in patients undergoing bariatric surgery.[93] This is specifically useful as dexmedetomidine does not cause respiratory depression. However, in patients undergoing spine deformity correction surgery, dexmedetomidine did not show any benefit of reducing postoperative opioid use.[94] The adverse effects of dexmedetomidine depend on the speed of the injection of the bolus dose. A bolus dose is often accompanied by initial hypertension, which is followed by hypotension and bradycardia. This can be attenuated by giving the bolus over 10–15 min.

Opioids

Opioids are the most effective drugs for the treatment of acute postoperative pain.[79] (Table 25.4) Opioids exert their analgesic effect through μ-opioid receptors. These receptors are located mainly in the CNS, although some are also present in the peripheral nervous system.[95] Pharmacology of opioids is further discussed in Chapter 47.

Opioids are known to cause several undesirable adverse effects such as nausea, vomiting, pruritus, ileus, OIH, tolerance, and respiratory depression, which limit the universal appeal of this most potent analgesic medication.

Opioids are one of the most versatile analgesics in terms of available routes of administration. They can be given enterally and parenterally, including IV, intramuscular (IM), intranasal, transdermal, sublingual, buccal, and neuraxial. The American Pain Society, in its recently updated guidelines, provides several recommendations in terms of routes of administration of opioids. These include preference of oral over parenteral route when possible, avoidance of IM injections, and use of IV PCA without a basal infusion when the parenteral route is necessary for opioid naïve patients.[3]

In a meta-analysis of forty-nine studies, PCA led to improved patient satisfaction and lower VAS pain intensity scores by nine points over the first 24 h (95% CI –13 to –5) and by 10 points over the first 48 h (95% CI –12 to –7) versus non-PCA. However, the amount of opioids consumed was higher in the PCA group, along with the incidence of pruritus. There was no difference in the length of hospital stay.[96]

TABLE 25.6 Intravenous Patient-Controlled Analgesia Regimens in Adults

Drug Concentration	Bolus Size* (Adult)	Lockout Interval (min)
Morphine (1 mg/mL)	0.5–2.5 mg	5–10
Fentanyl (0.01 mg/mL)	10–20 μg	4–10
Hydromorphone (0.2 mg/mL)	0.05–0.25 mg	5–10
Methadone (1 mg/mL)	0.5–2.5 mg	8–20
Meperidine (10 mg/mL)	5–25 mg	5–10
Alfentanil (0.1 mg/mL)	0.1–0.2 mg	5–10
Sufentanil (2 mcg/mL)	2–5 μg	4–10
Nalbuphine (1 mg/mL)	1–5 mg	5–15
Buprenorphine (0.03 mg/mL)	0.03–0.1 mg	8–20
Pentazocine (10 mg/mL)	5–30 mg	5–15

*Bolus doses should be titrated and based on clinical evaluation of the patient.
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IV PCA allows the clinician to compensate for variability in analgesic requirements as the patients can themselves control how much medication they receive. The lockout period, and the negative feedback loop, enhance the safety of PCA. However, excessive sedation or respiratory depression may occur when the negative feedback loop is violated.[97,98] Optimal settings for IV PCA administration of opioids for the management of postoperative pain are not known. Table 25.6 enumerates the common doses used for PCA. PCA should be weaned off, and oral medication started as soon as possible after the surgery. In summary, opioids are potent analgesics with potential dangerous adverse effects, and there has an impetus to limit the use of opioids postoperatively by supplementing several adjuncts.

Other pharmacologic agents, such as anti-depressants that include tricyclic anti-depressants (TCA) and selective serotonin reuptake inhibitors, and skeletal muscle relaxants such as baclofen, are primarily used for neuropathic pain and myofascial pain, respectively, and have been discussed elsewhere.

Summary

Multimodal analgesia is recommended for use in all surgical patients for postoperative pain relief. Opioids have long been the mainstay for pain relief. However, in recent years, there has been an emphasis on limiting narcotics to minimize the short and long term adverse effects. Several pharmacologic agents have shown great promise for postoperative analgesia in appropriate patient populations. NSAIDs in combination with acetaminophen have shown opioid-sparing properties and should be used in all patients without contraindications. IV lidocaine is a useful adjunct in patients undergoing abdominal procedures. Several other agents such as ketamine, gabapentinoids, and dexmedetomidine help in postoperative pain relief therapy with the ultimate goal of early recovery. The treating physician must effectively treat the patient's pain while limiting the pharmacologic side effects. Effective postoperative analgesia should be based on the patient's preference, expectation, comorbidities, and the surgery performed.

Key Points

- Postoperative pain assessment is a dynamic process.
- Pain should be assessed at regular intervals to guide therapy and assess for adverse effects.
- Commonly used pain scales such as VAS, NRS, and VRS can be used postoperatively, but their limitations should be kept in mind.
- Clinical evaluation of pain and functional assessment play an important role along with the pain scales to guide therapy.
- Multimodal regimens should be a part of the postoperative pharmacotherapy.

- A combination of NSAIDs and acetaminophen should be used in all patients without contraindications.
- IV lidocaine and ketamine are adjuncts that have shown benefit in appropriately selected patients.
- Opioids should be used as the last options, with the oral route being preferred over IV.
- IV PCA is the modality of choice for systemic administration of opioids.

Acknowledgments

The authors would like to thank Dr. Marie N. Hanna and colleagues who authored the previous chapter: "Postoperative Pain and Other Acute Pain Syndromes," authored by Dr. Marie N. Hanna and Colleagues in Practical Management of Pain, 5th edition, from which portions of this chapter have been transcribed and modified.

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Regional and Multimodal Treatments of Perioperative Pain

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Introduction

According to the American Society of Anesthesiologists (ASA) practice guidelines, acute pain in the perioperative setting is defined as the presence of pain in a surgical patient after a procedure.[1] The United States Institute of Medicine reported that despite advancements in perioperative pain control, 80% of patients who have surgery report postoperative pain, and 88% of these patients grade their severity as moderate, severe, or extreme.[2] Uncontrolled postoperative pain may be associated with slower recovery times, prolonged hospital length of stay, increased readmission rates, increased time before ambulation, increased hospital costs, and decreased patient satisfaction.[3,4] Suboptimal analgesia may also have organ-specific complications, including poor respiratory effort from splinting and atelectasis, increased incidence of myocardial ischemia, impaired wound healing, delayed gastrointestinal motility with prolonged ileus, psychological distress with anxiety, and lack of sleep.[5–7]

The concept of multimodal analgesia was introduced in 1993 to improve analgesia while concomitantly limiting opioid consumption and reducing the risk of opioid-related adverse effects.[8] This involves the combined use of regional anesthesia or local anesthetic infiltration, opioid medications, as well as various classes of non-opioid analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs), selective-cyclooxygenase-2 (COX2) inhibitors, N-methyl-D-aspartate (NMDA)-receptor antagonists, and antiepileptic drugs. Multimodal regimens may also be associated with the attenuation of the transition from an acute to a chronic postoperative pain state.[9,10]

Regional anesthesia techniques include both the central neuraxial blockade and peripheral nerve blockade, both of which are frequently used either intraoperatively as the primary anesthetic or perioperatively as adjunctive therapy to manage acute postoperative pain, reduce opioid consumption, improve satisfaction and quality of life, decrease hospital expenditures, and improve other postsurgical outcomes.[11] More recently, the use of ultrasonography in the fascial plane and neurolocalization has expanded the utilization of peripheral nerve blockade. Ultrasound guided regional anesthesia (UGRA) has been associated with improvements in performance time, reduction in doses of local anesthesia, and reductions in some complications (e.g. pneumothorax).[12]

This chapter discusses the use of regional anesthesia techniques to control postoperative pain in various surgical types. The authors support a multimodal approach to the management of postoperative pain control, and more details on pharmacologic treatment in a multimodal approach can be found in Chapter 25 and adjuvant medications are addressed in Chapter 54.

Pathophysiology of Acute Postoperative Pain

Surgical trauma activates peripheral nociceptors, including both high threshold neurons sensitive to mechanical, thermal, and chemical stimuli, which then relay afferent signals to the cerebral cortex via the spinal-thalamic tract.[13] However, these afferent signals may be amplified at various points along the pathway. The presence of inflammation at the site of surgical trauma leads to local release of neurochemical factors, which increase sensitivity to endogenous ligands and decrease the threshold of afferent nociceptive neurons (peripheral sensitization).[13] Inflamed neurons may also alter the expression of sodium channels, which may show an increased proportion of tetrodotoxin-resistant channels, which have greater spontaneous ectopic activity.[13] Surgical insults may also lead to increased neuronal excitability within the spinal cord because of a persistent signal from peripheral afferent nociceptive neurons (central sensitization).[14,15] The nociceptive afferent neurons synapse in laminae I and II of the dorsal horn, and signals at this location may be modified as wide dynamic range neurons decrease their threshold for activation and widen their receptive field, and NMDA receptor activation is increased.[13] This mechanism leads to a decrease in pain threshold at the surgical site (primary hyperalgesia) as well as surrounding uninjured tissue (secondary hyperalgesia). Thus even a tactile stimulus that is not painful may elicit a painful response (allodynia) in postsurgical patients because of sensitization.

Biochemically, surgical insult leads to the release and upregulation of a pro-inflammatory cytokine profile, particularly an increase in interleukin-1b (IL-1b) and peripheral COX-2. Furthermore, IL-1b induces COX-2 in the central nervous system because of the presence of peripheral inflammation.[16] There are also humoral signals released from the inflamed surgical tissue that cross the blood-brain barrier directly and induce central COX-2. Thus while peripheral-acting COX-2 inhibitors and local anesthetic blockade may work peripherally to block COX-2 expression and provide analgesia, only central-acting COX-2 inhibitors block the expression of central COX2.[17,18]

Preoperative Assessment and Informed Consent

A thorough patient evaluation, including history, medication review, and physical examination, is vital prior to perioperative anesthesia and analgesia. Preoperative pain levels, certain age groups, anxiety, and depression may be associated with heightened postsurgical pain.[19] In contrast, in high-risk groups such as those with chronic pain (please refer to Chapter 36), regional anesthesia as an adjunct to analgesia may be beneficial. In some patients, regional anesthetic techniques may be inappropriate. For instance, in patients with a history of severe respiratory disease undergoing shoulder surgery, interscalene blockade may be disadvantageous because it will lead to phrenic nerve blockade and potential for subsequent respiratory decompensation.[20] History should also be elicited on preexisting nerve injury, whether it is localized to the site of the surgical procedure, its chronicity, and its temporal change (e.g. recent improvement or worsening nerve function). Preexisting nerve damage or deficit is considered a relative contraindication to regional anesthesia. In some instances, if the patient's preexisting neuropathy is stable, regional anesthesia may be pursued after a thorough discussion of the risks. The clinician should convey to a patient that a preexisting nerve injury may serve as a priming event ("first hit") and that any sequential insults ("second hit") can culminate in an increased risk of further nerve damage compared to the general population (please refer to Chapter 35).[21]

As part of a multimodal approach to pain management, preventive analgesia should also be considered. Preventive analgesia is defined as analgesia administration prior to the occurrence of painful stimuli, which may prevent or reduce subsequent intraoperative and postoperative pain and analgesic requirements.[22] Preventive analgesic techniques involve the use of pharmacologic agents that reduce the activation of nociceptors by blocking or decreasing receptor activation. Multiple studies have demonstrated that patients receiving preventive analgesia experience a decrease in total analgesic consumption (please refer to Chapter 24).[23,24]

After ensuring that the patient is a good candidate for regional anesthesia, the clinician performing the regional anesthetic procedure should provide thorough informed consent. This is not only important from a medicolegal standpoint but also improves ethical practice that respects the patient's autonomy and supports the patient-physician relationship. Studies in the regional anesthesia and perioperative setting demonstrate that patients desire to know the risks, benefits, and alternatives for the anesthetic modality that they will receive.[25,26]

The utilization of regional anesthesia checklists is also an important part of the pre-procedural period. Checklists typically comprise of patient identification, review of allergies and anticoagulation, confirmation of informed consent and marked site, obtaining the necessary equipment and labeled drugs, application of standard ASA monitors, establishment of intravenous access, administration of sedation and oxygenation if indicated, preparation of site using sterile technique and use of gloves and mask, and performing a verbal "time out."[27] By implementing a regional anesthesia-specific pre-procedural checklist, studies have demonstrated a lower incidence of procedures being performed on the wrong side.[28]

After administration of an analgesic, the clinician must follow up with the patient's response, which is typically performed routinely after surgery using an 11 point (0–10) pain assessment scale or other pain measurement tools. Clinicians should assess patient satisfaction and tolerance of the current level of pain and whether more analgesia would be desirable. This patient-centered approach with reliable follow up of analgesic response and good communication is crucial for successful perioperative pain management.

Multimodal Analgesia

Multimodal analgesia involves the use of multiple medications to treat pain, each with different mechanisms of action that may have synergistic or additive effects when combined.[29] The combination of different types of analgesics captures analgesic efficacy at optimal doses while minimizing side effects from any one analgesic, particularly undesirable effects of opioids such as nausea, vomiting, and respiratory depression. It is important to note that the use of local anesthetic alone to block the neuronal pathways is not always sufficient and does not decrease the humoral biochemical responses that occur following surgery; systemic pharmacologic agents may be required to attenuate the humoral biochemical and inflammatory postsurgical response.[17] In addition to opioids and regional anesthetic techniques, examples of medications commonly utilized during the perioperative period with different mechanisms of action include NSAIDs, acetaminophen, ketamine, α-2-agonists, glucocorticoids, gabapentinoids, and duloxetine (Table 26.1).[29] A sample multimodal analgesic plan is provided for perioperative management in Table 26.2.

Enhanced Recovery After Surgery (ERAS) Protocols

Enhanced recovery after surgery (ERAS) perioperative care pathways, previously known as "fast-track" programs, are designed to achieve early recovery after surgery by maintaining preoperative organ function and decreasing the stress response associated with surgery.[30] Studies demonstrate that implementation of ERAS pathways lead to a reduction in complications, decreased hospital stay, improved cardiopulmonary function, improved bowel function, and earlier resumption of physical and regular activities.[31] The main elements of ERAS comprise providing preoperative counseling, optimizing nutrition, avoiding perioperative fasting, implementing multimodal analgesic pathways (regional and non-opioid analgesia), and early mobilization.[30] A sample ERAS protocol pathway is provided in Table 26.3.

Drug Toxicity

A life-threatening event from local anesthetic medication is local anesthetic systemic toxicity (LAST), which currently has an estimated incidence of 0.03% or 0.27 events per 1,000 peripheral blocks.[32] While accidental injection of a local anesthetic directly into a vessel is a well-known cause of LAST, other predisposing factors may include increasing use of continuous catheter techniques, high volume fascial plane blocks, multiple peripheral nerve blocks in the same patient, and utilization of tumescent anesthesia. It is recommended that the proceduralist adhere to guidelines on the maximum recommended local anesthetic dose.[33]

There has also been a growing use of non-local anesthetic adjuvants in regional nerve blocks, including epinephrine, α-2-agonists, neostigmine, and steroids (e.g. dexamethasone).[34] Data on the additional analgesic benefit are mostly lacking, and caution is advised when using certain adjuvants. The addition of α-2-agonists (e.g. clonidine) may be associated with bradycardia and hypotension.[34] Gastrointestinal side effects may be frequent with neostigmine.[34]

TABLE 26.1 Systemic Opioid and Non-opioid Analgesic Medications

Medication Class	Example of Drugs	Mode of Delivery	Analgesic Ceiling	Side Effects	Comments
Acetaminophen		PO, IV	Yes	Hepatotoxicity, pruritus, rash	
Non-selective NSAIDs	Ibuprofen, naproxen, meloxicam	PO, IV, IM	Yes	Platelet inhibition, GI bleeding risk, renal and hepatotoxicity, inhibition of bone healing and osteogenesis, cardiovascular risk (MI, stroke)	Provides opioid-sparing analgesia. Consider concurrent PPI use
COX-2 inhibitor	Celecoxib	PO	Yes	Renal and hepatotoxicity, cardiovascular risk (MI, stroke)	Provides opioid-sparing analgesia. Caution is advised in those with cardiovascular risk factors
Opioid	Fentanyl, morphine, hydromorphone	PO, IV, IM, SQ, NA, PNB, TD, TM, IN	No	Nausea/vomiting, respiratory depression, sedation, pruritus, constipation, urinary retention, dizziness	Choice of the agent should depend on potency and the expected duration of action. Use shorter-acting agents (e.g. fentanyl) for shorter hospital LOS or same-day discharge, and reserve longer-acting opioids (e.g. hydromorphone) for inpatients or opioid tolerant patients
Tramadol and tapentadol		PO, IV	Yes	Nausea/vomiting, dizziness, sedation, headache	Low affinity for opioid receptors; inhibits serotonin reuptake and may precipitate serotonin syndrome; contraindicated in patients taking MAOi; may lower the seizure threshold and caution is advised in those with a history of seizures; adjuvant in neuropathic pain
Anti-convulsant/ Gabapentinoid	Gabapentin, pregabalin	PO	Unknown	Dizziness, sedation, fatigue, tremor, ataxia, impairment in memory, edema, weight gain, vision abnormalities	Provides opioid-sparing analgesia, useful in both acute postoperative pain and chronic antihyperalgesia; adjuvant in neuropathic pain
NMDA Antagonist	Ketamine, methadone (opioid with NMDA receptor antagonism)	IV, IM, PO	Yes	Confusion, disorientation, dissociation, nausea/ vomiting, sedation, ataxia, double-vision	Provides opioid-sparing analgesia; may attenuate chronic pain after surgery; implicated in preventing opioid-induced hyperalgesia; more effective in use in opioid tolerant patients but benefits seen in those opioid naïve
α-2-agonist	Dexmedetomidine, clonidine	PO, IV, IM, IN	Yes	Changes in blood pressure and heart rate (usually hypotension, bradycardia), nausea/ vomiting	Suppression of opioid-withdrawal symptoms, preserves minute ventilation
Corticosteroid	Dexamethasone	IV, PO	Unknown	Edema, hypertension, elevated blood glucose, confusion, and delirium	Place in pain therapy is unclear, but evidence suggests analgesic effect as an adjuvant for opioid tolerance

COX, Cyclooxygenase; *IM*, intramuscular; *IV*, intravenous; *PO*, per oral; *SQ*, subcutaneous; *TD*, transdermal; *PNB*, peripheral nerve block; *NA*, neuraxial; *TM*, transmucosal; *IN*, intranasal; *NSAID*, nonsteroidal anti-inflammatory drug; *MI*, myocardial infarction; *GI*, gastrointestinal; *LOS*, length of stay; *MAOi*, monoamine oxidase inhibitor; *PPI*, proton pump inhibitor.

TABLE 26.2 Multimodal Analgesia Pathway for Cardiac Surgery

Preoperative
Acetaminophen (paracetamol) 1000 mg PO
Caffeine 200 mg PO if the patient reports regular caffeine intake[a]
Celecoxib 400 mg PO (administered if aged 18–64 years and glomerular filtration rate >50 mL/min)[b]
Consider oxycodone immediate release 5 or 10 mg PO (administered if aged 18–64 years) in patients with preoperative opioid dependence
Intraoperative
Utilization of regional anesthetic techniques (may consider surgeon-administered wound infiltration and various PNB techniques including interscalene, anterior suprascapular, or supraclavicular block with supplementation of cervical plexus)
Consider dexamethasone up to 0.2 mg/kg IV
Consider dexmedetomidine 0.5 mcg/kg/min IV
Postoperative
Re-dose acetaminophen (paracetamol) 1000 IV every 6 hours until the patient starts taking oral medications
Ketorolac 7.5–15 mg IV every 6 hours up (up to five doses maximum; adjusted for age, creatinine clearance, and weight); avoid if age > 70 or creatinine clearance < 30 mL/min)[b]
Fentanyl 25 mcg IV prn or hydromorphone 0.2 mg IV prn for pain score> four
Oxycodone 5–10 mg PO every 4 hours prn and/or hydromorphone 1–2 mg PO every 4 hours prn when taking oral medications
Ketamine 10 mg IV every 5 minutes for severe pain (7–10) and consideration of initiating ketamine infusion 0.1–0.3 mg/kg/h for persistent severe postoperative pain

[a]There is currently weak evidence for preoperative caffeine. Source: Hampl et al. Perioperative administration of caffeine tablets for the prevention of postoperative headaches. *Can J Anaesth*. 1995;42(9):789–792.

[b]Careful patient selection for NSAID therapy is warranted; in certain patient populations undergoing colorectal surgery (e.g. Crohn's disease and ulcerative colitis), NSAIDs may be contraindicated.

PO, Mouth; IV, intravenous; *PCA*, patient-controlled analgesia; *prn*, as needed; *GFR*, glomerular filtration rate; *PNB*, peripheral nerve blockade.

A sample multimodal pathway adapted from Panchamia et al. A 3-arm randomized clinical trial comparing interscalene blockade techniques with local infiltration analgesia for total shoulder arthroplasty. *J Shoulder Elbow Surg*. 2019;28(10):e325-e338.

Regional Anesthesia Techniques

The aforementioned ERAS pathways and the regional anesthetic techniques described below should be tailored to the individual patient while keeping in mind the surgical type, side effects of the individual medications, and the patient's comorbidities.[35] The regional anesthetic blocks described below include neuraxial regional techniques as well as peripheral/perineural nerve blocks commonly performed in the perioperative setting and may serve as rescue blocks for postoperative pain management in the wards and beyond. The goal of this section is not to provide a comprehensive list but instead provide examples of common regional anesthetic blocks and to appraise the evidence in the literature for their analgesic efficacy in the perioperative setting.

Neuraxial Analgesia

Generally, neuraxial techniques provide better analgesia than systemic opioids and have the advantage of decreasing adverse perioperative pathophysiology (e.g. stress response) while improving patient outcomes. For instance, continuous epidural infusion has been shown to be associated with decreased pulmonary,[36] cardiovascular,[37–39] and gastrointestinal[40] complications in high-risk patients after high-risk procedures. Below, we describe the spinal (intrathecal), epidural, and caudal anesthesia techniques.

Spinal Analgesia

While intrathecal local anesthetic administration is often used as the primary anesthetic for many surgeries (e.g. cesarean deliveries, certain abdominal procedures) instead of general anesthesia, the focus of this section will be on intrathecal medications for postoperative analgesia only. Intrathecal opioids are potent, centrally acting analgesic drugs and are commonly administered to provide intraoperative and postoperative analgesia.

When administering neuraxial opioids, it is important to consider the lipophilic properties of opioids. Studies have demonstrated that the liposolubility of intrathecal opioids is inversely proportional to spinal selectivity and spinal-mediated analgesia, which is higher for hydrophilic opioids than for other more lipophilic opioids.[41] While all opioids administered intrathecally produce some degree of spinal-mediated analgesia, hydrophilic opioids provide primarily spinal-mediated analgesia, while lipophilic opioids tend to provide analgesia via either a spinal or systemic mechanism.[42] Hydrophilic opioids, including morphine and hydromorphone, remain in the cerebrospinal fluid (CSF) for a long duration and can produce a delayed but longer duration of analgesia. Because of this property, hydrophilic opioids may have a higher incidence of delayed respiratory depression because of greater CSF spread.[43] Intrathecal morphine may lead to severe respiratory depression lasting up to 24 hours.[43] The respiratory

TABLE 26.3 Enhanced Recovery Pathway for Colorectal Surgery

Preoperative
Fluid and carbohydrate loading,[a] and avoidance of prolonged fasting
Caffeine 200 mg PO if the patient reports regular caffeine intake
Antibiotic prophylaxis
Thromboprophylaxis
Acetaminophen (paracetamol) 1000 mg PO
Celecoxib 200–400 mg PO (adjusted for age, creatinine clearance, and weight)
Consider granisetron 1 mg IV or scopolamine patch if the patient reports a history of severe PONV
Intraoperative
Administration of short-acting anesthetic agents (e.g. fentanyl IV or remifentanil IV)
Utilization of regional anesthetic techniques (may consider neuraxial analgesia, liposomal bupivacaine wound infiltration, and various truncal blocks such as TAP blocks and rectus abdominis sheath block)
Avoidance of excessive fluid administration
Maintenance of normothermia
Re-dose Acetaminophen (paracetamol) 1000 IV if 6 hours since preoperative dose
Ketorolac 7.5–15 mg IV (adjusted for age, creatinine clearance, and weight) at skin closure; avoid if age > 70 or creatinine clearance < 30 mL/min)
Avoidance of surgical drain placement
PONV prophylaxis: dexamethasone 4–8 mg IV at induction, ondansetron 4 mg IV at the end of the case (if the patient has two or more PONV risk factors,[b] consider the addition of droperidol 0.625 mg IV or promethazine 12.5 mg IV or haloperidol 1–2 mg IV at the end of the case)
Postoperative
Maintenance of continuous regional anesthetic technique (e.g. epidural catheter)
Early removal of urinary catheter
Early oral nutrition
Bowel regimen and agents to promote stimulation of gut mobility
Early mobilization
Use of non-opioid analgesics: Re-dose acetaminophen (paracetamol) 1000 IV every 6 hours until the patient starts taking oral medications Re-dose ketorolac 7.5–15 mg IV every 6 hours up (up to five doses maximum; adjusted for age, creatinine clearance, and weight) at skin closure; avoid if age > 70 or creatinine clearance < 30 mL/min)
Oxycodone 5–10 mg PO every 4 hours prn when taking oral medications

[a]Source describing evidence on preoperative carbohydrate loading. Bilku et al. Role of preoperative carbohydrate loading: a systematic review. *Ann R Coll Surg Engl.* 2014;96(1):15–22.

[b]PONV risk factors include female sex, young to middle age, history of PONV or motion sickness, and non-smoking status.

PO, Mouth; *IV*, intravenous; *PCA*, patient-controlled analgesia; *prn*, as needed; *PONV*, postoperative nausea, and vomiting; *TAP*, transversus abdominis plane.

depression after intrathecal morphine administration usually follows a biphasic pattern with an initial onset in the first 1–3 hours and a late-onset at 6–12 hours because of their hydrophilic nature and cephalad spread.[43] On the other hand, lipophilic opioids, such as fentanyl and sufentanil, have a faster onset of action but a shorter duration of analgesia because of more rapid diffusion from CSF.[41] Common side effects of all intrathecal opioids include pruritus in up to 60% of patients,[44,45] nausea and vomiting in over 50% of patients,[46] and urinary retention in up to 80% of patients.[47]

There is limited evidence on the use of other intrathecal medications for postoperative pain control, including α-2-agonists,[48] steroids,[49] and neostigmine.[50] A randomized clinical study by Sarma and colleagues showed that a low dose of intrathecal dexmedetomidine or clonidine with bupivacaine produced a shorter onset and longer duration of motor and sensory blockade than bupivacaine alone in lower limb surgeries.[48] Another prospective, double-blind study[51] showed that intrathecal dexmedetomidine with bupivacaine provided earlier onset of sensory and motor block, longer duration of analgesia, and preserved hemodynamic stability compared to bupivacaine alone in infraumbilical surgeries. Of all adjuvants for neuraxial analgesia, only clonidine is approved by the FDA.[52] Future well-designed randomized controlled trials (RCTs) assessing postoperative analgesia with intrathecal adjuvant medications are warranted.

In summary, intrathecal administration of lipophilic opioids produces short-term analgesia for approximately 1–4 hours and may be helpful for immediate postoperative pain. Although hydrophilic intrathecal opioids provide longer duration analgesia (for up to 24 hours) useful for more invasive and painful surgeries, we recommend that it be limited to patients expected to remain hospitalized in an appropriately monitored setting for at least one postoperative day.

Epidural Analgesia

Continuous epidural analgesia offers postoperative pain management for a longer duration than a single injection spinal injection and analgesia superior to systemic opioids.[53] In terms of pharmacokinetics, medications placed in the epidural space must cross the dura prior to reaching the spinal cord.[54] In addition, because of the high vascularity of the epidural space, there may be a significant redistribution of epidural medications into the systemic circulation.[54] Furthermore, the presence of epidural fat may serve as a repository for lipophilic drugs.[54]

Notably, compared to the intrathecal space, significantly larger amounts of medication need to be delivered via the epidural route to obtain equivalent analgesic efficacy because diffusion of drugs across the dura is concentration and time dependent.[54] This pharmacokinetic concept is complex and involves inherent drug properties, primarily lipophilicity. For instance, lipophilic opioids (fentanyl and sufentanil) readily cross the dura to reach spinal cord receptors, whereas hydrophilic opioids (morphine) would cross the dura more slowly; thus when calculating the epidural dose for a medication that is equianalgesic to the intrathecal route, a higher epidural dose would be required for hydrophilic medications than for lipophilic medications. As a general rule of thumb, 10 mg of epidural morphine (hydrophilic opioid) would be equianalgesic to 0.1 mg of intrathecal morphine (10:1 ratio), whereas 33 mcg of epidural fentanyl would be equianalgesic to 6–10 mcg of intrathecal fentanyl (5:1 to 3:1 ratio).[55] However, further well-designed dosing studies are warranted to validate these findings.

Typically, epidural local anesthesia with or without opioids offers better physiologic benefits after most surgeries than opioids alone and may decrease opioid-related side effects. The choice of local anesthetic may vary based on provider preference, but a local anesthetic with a longer duration of action with preferential sensory blockade and limited motor blockade is preferable for postoperative analgesia.[56] However, in certain circumstances, such as persistent hypotension, epidural opioids alone may be more advantageous because of sympathectomy often associated with epidural local anesthetic.

When initiating epidural analgesia, small epidural bolus doses (5–10 mL) are usually administered first over a short period of 5–10 minutes to achieve an adequate depth of analgesia prior to initiating a continuous epidural infusion rate that can be titrated to effect. Furthermore, different delivery modes of epidural analgesia may be instituted, including fixed continuous infusion or patient-controlled epidural analgesia (PCEA). Similar to intravenous patient-controlled analgesia (PCA), PCEA allows analgesic requirements to be individualized to the needs of the patient and improves patient satisfaction.[57,58] Various combination settings may be employed, including continuous epidural infusion rate with PCEA together or a programmed intermittent epidural bolus technique with PCEA.

Similar to the intrathecal route, there is limited evidence of certain epidurally delivered adjuvant medications. Clonidine may provide analgesia via the epidural route by activating the descending noradrenergic pathway but may be limited by hypotension, bradycardia, and sedation.[59] Epinephrine may increase the intensity of sensory blockade when administered with a local anesthetic.[60]

In summary, continuous epidural analgesia provides superior analgesia and better patient outcomes than intravenous opioids and can provide postoperative pain control with epidural local anesthetic alone or a combination of epidural local anesthetic and opioids. Continuous infusion and other delivery modes can provide prolonged postoperative analgesia and may be titrated to an analgesic effect.

Caudal Analgesia

Caudal analgesia involves injection through the sacrococcygeal ligament with entrance into the epidural space.[61] There is limited utility of caudal analgesia for acute postoperative pain control in adult patients because it is more technically challenging to perform caudal injection compared to lumbar or thoracic epidural blocks. Caudal analgesia is useful in the pediatric population and provides excellent postoperative analgesia for inguinal hernia repair, urologic interventions (e.g. circumcision, hypospadias correction, orchidopexy), anal atresia repair, and lower extremity surgeries.[62,63] Additional details on pediatric analgesia may be found in Chapter 28.

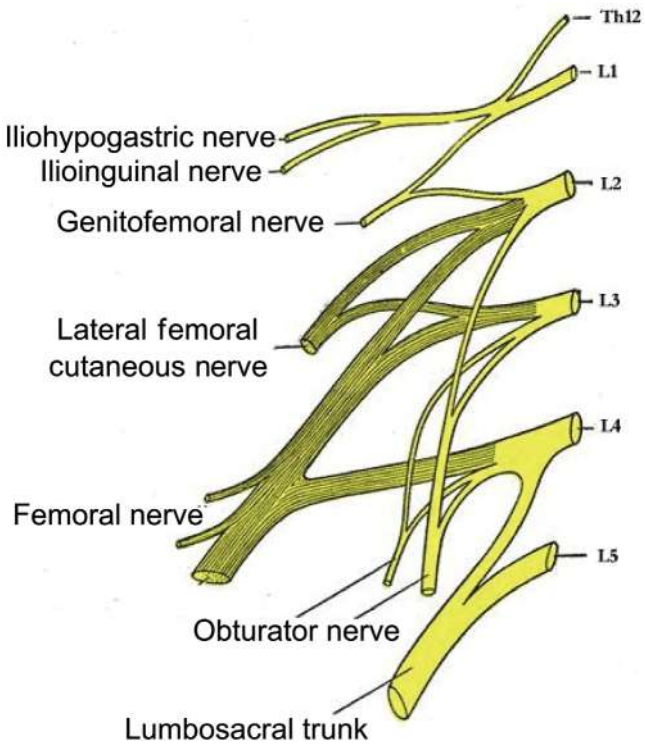
Complications With Neuraxial Techniques

The most common risks from neuraxial analgesia include hypotension, nausea and vomiting, and back pain.[64] Transient neurological syndrome (TNS) is severe lower back pain localized in the buttocks and lower extremities after recovery from spinal anesthesia with no evidence of localized nerve damage.[65] Risk factors for TNS include intrathecal lidocaine administration, lithotomy position, and ambulatory surgery.[65–67] Postdural puncture headache (PDPH) is because of lumbar puncture with subsequent CSF leak through the puncture site causing symptoms related to traction of pain-sensitive central nervous system structures.[68] To decrease the risk of PDPH, it is recommended to use a non-cutting needle.[68] When utilizing a pencil-point spinal needle, a meta-analysis by Zorrilla-Vaca et al. demonstrated no difference in PDPH rates between 22-gauge and 25-gauge needles. Thus this study concluded that providers might consider using larger-caliber pencil-point spinal needles in all but the youngest patients to maximize technical proficiency instead of risking a failed spinal anesthetic by using a smaller sized spinal needle.[68] Epidural catheters may be misplaced or may migrate after placement,[69] leading to ineffective or inadequate analgesic coverage. Epidural placement closer to one side may result in a one-sided blockade with inadequate coverage of the contralateral side. Inadvertent placement of an epidural catheter in the subdural space may lead to unpredictable block characteristics, including an inappropriately high block because of extensive spread, delayed onset, segmental distribution, and potential for motor blockade.[70] The feared complication is total spinal anesthesia, which occurs if excess local anesthetic is administered intrathecally, leading to coma, paralysis, hypotension, bradycardia, and apnea.[71] Other rare adverse events include infection, hematoma, and nerve injury.[69]

Peripheral Nerve Blockade

Utilization of peripheral nerve blockade in the perioperative setting is associated with adequate pain control, reductions in hospital length of stay, decreased hospital costs, better rehabilitation, and other improved postsurgical outcomes.[72,73] Peripheral nerve blockade can be established with a single injection of local anesthetic or with a continuous infusion through a perineural catheter. A perineural catheter with continuous infusion may provide equivalent analgesia to an epidural for certain surgeries while carrying fewer side effects than epidural analgesia.[74] Patients may be discharged home with continuous local analgesic medications delivered via a perineural catheter and may remove the perineural catheter themselves without requiring a hospital visit.[75,76]

Techniques for peripheral nerve blockade localization include paresthesia, peripheral nerve stimulator, and UGRA, although there has been a recent preference for UGRA. UGRA may be associated with a greater block success rate, faster onset of sensory block, fewer needle passes, and less discomfort during the block.[77,78] Lidocaine and mepivacaine are commonly used to provide short to intermediate duration peripheral nerve blockade.[79] In contrast, bupivacaine, levobupivacaine, and ropivacaine are preferred for longer duration peripheral nerve blockade.[80,81] Other adjuvant medications are not currently approved but are commonly added to local anesthetics, including epinephrine[82] (detects inadvertent intravascular uptake, denser and prolonged blockade related to vascular constriction) and clonidine (prolongs the duration of analgesia with added risks for hypotension and cardiac arrhythmias).[83,84] Below, we discuss various peripheral nerve blocks of the upper extremity, lower extremity, and trunk.



• **Figure 26.1** Lumbar Plexus. (Adapted from 20th United States edition of Gray's Anatomy of the Human Body [No copyright needed as the image is available in the public domain].)

Lower Extremity Peripheral Nerve Blocks

The ventral rami from the lumbar plexus (L1–4) and the sacral plexus (L4–5, S1–3) provide innervation to the lower extremity.[85] The specific nerves derived from the lumbar plexus (Fig. 26.1) include the lateral femoral cutaneous nerve (L2–3), obturator nerve (L2–4), femoral nerve (L2–4); the lumbar plexus also gives rise to the iliohypogastric, ilioinguinal, and genitofemoral nerves, which innervate the inguinal and genital areas.[85] The sciatic nerve (L4–5, S1–3) is derived from the sacral plexus.

Lumbar Plexus Block

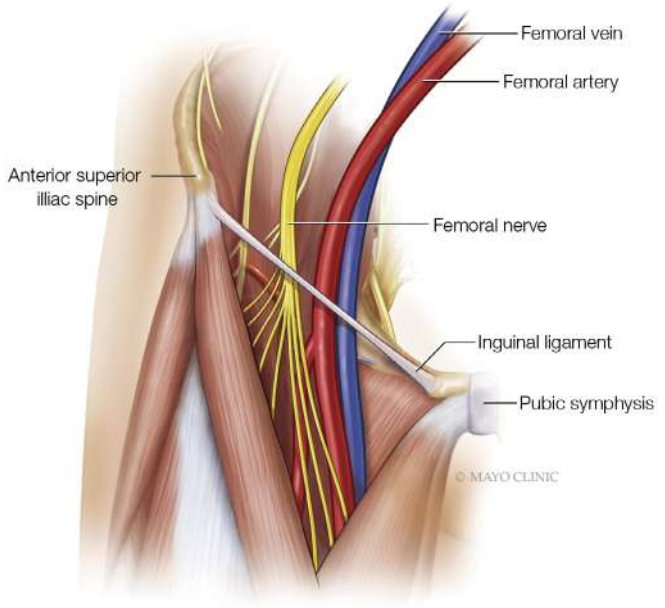
The lumbar plexus is triangular-shaped, with the femoral nerve situated in the middle, the lateral cutaneous femoral nerve situated laterally, and the obturator nerve situated medially in the plexus.[86] When the local anesthetic is injected within the psoas muscle, there is cephalad spread of the local anesthetic to the lumbar nerve roots. Hence, the term "psoas compartment" block is often used interchangeably with "lumbar plexus block."[86,87] Since lumbar plexus blockade covers both the femoral and obturator nerves, it provides surgical anesthesia and postoperative analgesia for surgeries of the hip joint (e.g. total hip arthroplasty, hip arthroscopy) and knee joint (total knee arthroplasty, multi-ligament reconstruction, and ligament repair surgeries) in conjunction with a sacral plexus block.[88,89] In certain invasive knee surgeries where coverage from the obturator nerve is not required, it may be technically easier to perform a femoral nerve block instead of a lumbar plexus block.[90]

Compared to hip surgery patients who did not receive any nerve blockade, those who received lumbar plexus blockade experienced decreased intraoperative blood loss, decreased postoperative opioid consumption, improved patient satisfaction, earlier postoperative ambulation, and improved participation in physical therapy and rehabilitation.[89,91,92] Compared to epidural analgesia, continuous lumbar plexus blockade may be associated with less motor blockade, faster time to ambulation, and fewer overall complications.[93] Thus the lumbar plexus block may play a pivotal role in ERAS protocols for hip surgery.

By itself, the lumbar plexus block is unlikely to provide complete anesthesia for hip surgeries because the sacral plexus provides innervation to the posteromedial capsule of the hip.[94] Compared with general anesthesia, a combination of lumbar plexus and parasacral blocks for hip surgeries in elderly patients may be utilized as the primary anesthetic and is associated with less hypotension, shorter hospital length of stay, fewer intensive care unit admissions, and improved patient satisfaction.[95,96]

Femoral Nerve Block

The femoral nerve is the largest nerve from the lumbar plexus.[97,98] It travels in the groove between the psoas muscle and iliacus muscle, passes under the inguinal ligament, and presents at the femoral triangle where it runs laterally to the femoral vessels (Fig. 26.2).[97,98] The femoral nerve then divides into anterior and posterior terminal branches, with anterior branches providing mainly cutaneous innervation and posterior branches providing primarily motor innervation.[99] The femoral nerve provides motor and sensory innervation to the skin and muscles of the anterior compartment of the thigh (e.g. quadriceps muscle), while its terminal branch (saphenous nerve) provides sensory innervation only to the medial portion of the leg from below the knee to the



• **Figure 26.2** Femoral Nerve. (Courtesy of Mayo Clinic.)

big toe.[99] Given the proximity of the femoral nerve to the artery, which is located in a separate sheath about 1 cm apart, accidental intravascular injection and hematoma formation are potential complications during blockade.[100]

Femoral nerve blockade provides excellent postoperative analgesia for mid-femur and knee surgeries, such as total knee arthroplasty (TKA), and may also be a satisfactory analgesic alternative to posterior lumbar plexus blockade for hip arthroplasty.[101] Because blockade occurs distally to the lumbar plexus, there is preservation of the hip flexion and hip adduction function, but patients cannot perform knee extension (function of quadriceps muscle).[102] While femoral nerve blockade may be utilized as the sole regional analgesic modality for knee surgeries, it is commonly supplemented with sciatic nerve blockade to provide coverage of the posterior aspect of the knee (e.g. TKA surgery, anterior cruciate ligament [ACL] surgery with hamstring autograft) or for below the knee procedures.[103,104] Similarly, if more proximal coverage of the medial compartment of the knee is required, supplementation with an obturator nerve block may be desirable.[105]

Compared to systemic pharmacologic therapy alone in patients undergoing TKA, studies and systematic reviews demonstrate that both single injection and continuous femoral nerve blockade are associated with superior analgesia.[73,106,107] Patients receiving femoral nerve blockade may also experience faster time to ambulation, improved knee flexion, reduced intraoperative and postoperative bleeding, quicker recovery, and decreased hospital length of stay.[73,106–108] Compared with surgeon-performed periarticular injection after TKA, continuous femoral nerve blockade may be associated with lower opioid consumption and improved recovery after six weeks.[109] Studies have also compared epidural analgesia versus continuous femoral nerve blockade after TKA, demonstrating that femoral nerve blockade provides equivalent postoperative analgesia, rehabilitation indices, and hospital duration of stay, but with fewer side effects (e.g. pruritus, postoperative nausea and vomiting, and dizziness).[110–112]

Saphenous Nerve Block

The saphenous nerve is a distal sensory branch of the femoral nerve that innervates the medial portion of the leg, medial calf, medial malleolus, and anteromedial foot.[113,114] Depending on the nature of the surgery and the location where analgesia is desired, the saphenous nerve may be blocked in several different locations, including perifemoral, subsartorial, transarterial, block at the medial femoral condyle, below the knee, paravenous approach, and at the medial malleolus.[115] Below, we focus on the subsartorial approach and discuss the saphenous nerve block at the medial malleolus in the "ankle block" section.

The subsartorial approach to the saphenous nerve block (proximal, mid-thigh approach in the middle third of the thigh) may be performed in patients who have undergone knee arthroplasty. This technique is often called the "adductor canal block." The adductor canal is a triangular-shaped canal with borders formed by the vastus medialis laterally, adductor longus or magnus medially, and roofed medially by the sartorius muscle, and can be visualized as a round hyperechoic structure anterior to the femoral artery using ultrasonographic guidance.[116,117] Given that femoral nerve blockade leads to quadriceps muscle weakness and impairment of early mobilization, the acute pain interventionalist now more often substitutes the adductor canal block for postoperative analgesia for TKA because it provides sensory blockade while sparing quadriceps strength and facilitating rehabilitation.[118] Similarly, a meta-analysis on patients undergoing ACL repair also demonstrated that adductor canal blockade is associated with similar analgesic requirements and short-term preservation of quadriceps muscle strength (24–48 hours) compared to femoral nerve blockade.[119] However, reports of significant quadriceps muscle weakness from local anesthetic spread in an adductor canal block have been described.[120] Risk factors, including advanced age, elimination-related activities (e.g. while in the bathroom, going to and from the bathroom, while using bedside commode), and intermediate phase of recovery (late postoperative day one to postoperative day three), also make patients vulnerable to fall after orthopedic surgery, and fall prevention strategies should be an institutional priority.[121]

Fascia Iliaca Block

The fascia iliaca is derived from fascicular aponeurotic sheets of the psoas and iliacus muscles. It is hypothesized that since there are multiple peripheral nerves enclosed within the fascia iliaca compartment in close proximity, including the femoral, lateral femoral cutaneous, genitofemoral, and obturator nerves, a high volume injection of local anesthetic may block all these peripheral nerves with one injection along this fascial plane.[122,123] Studies have demonstrated that the fascia iliaca block may provide adequate analgesia after hip, knee, and femoral shaft surgery.[124,125] A loss-of-resistance technique may be used to block the fascia iliaca compartment. However, studies have demonstrated that ultrasound guidance increases block success rates and the percentage of patients experiencing blockade of the femoral, obturator, and lateral femoral cutaneous nerves.[126] Compared to systemic opioid therapy alone, fascia iliaca block may provide superior pain relief postoperatively after hip surgery[127–130] and femoral fracture surgery.[131]

Sciatic Nerve Block

The sciatic nerve is the largest of the peripheral nerves supplying the lower extremity and provides innervation to the posterior thigh, leg below the knee, except for its medial portion (supplied

by the saphenous nerve), and the foot. It is commonly blocked either via the subgluteal or popliteal approach (discussed below). Sciatic nerve blockade provides excellent coverage for all foot and ankle surgeries[132,133] and is often performed in conjunction with femoral or lumbar plexus blocks for postoperative analgesia after hip or knee surgeries.[104] However, sciatic nerve blockade is often accompanied by hamstring muscle weakness, limiting its utility in many distal foot and ankle surgeries where postoperative weakness is undesirable.[134] Phantom limb pain following below-knee or above-knee amputation may significantly improve with continuous sciatic nerve blockade.[135]

Compared to femoral nerve blockade alone, both a femoral nerve block and sciatic nerve block provide superior postoperative analgesia and reduce postoperative opioid consumption.[136,137] Furthermore, a meta-analysis revealed that patients undergoing TKA who received sciatic nerve blockade as an adjunct to femoral nerve block reported lower postoperative pain scores and consumed fewer opioids up to 24 hours postoperatively compared to those who received femoral nerve blockade with local infiltration analgesia.[138]

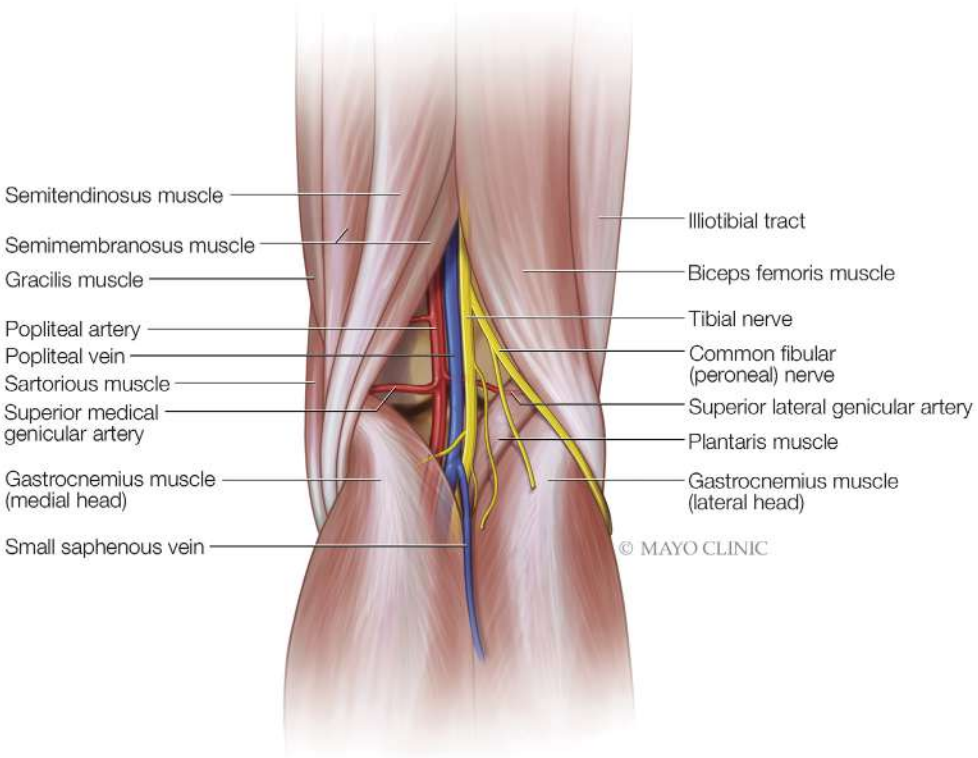
Popliteal Sciatic Nerve Block

The popliteal fossa is bordered superomedially by the semimembranosus and semitendinosus muscles, superolaterally by the biceps femoris, and inferiorly by the two heads of the gastrocnemius muscle. Within the popliteal fossa, the sciatic nerve is located posterolateral to the popliteal vessels (Fig. 26.3). Compared to the subgluteal approach to sciatic nerve blockade, the more distal location of popliteal sciatic nerve blockade preserves hamstring muscle strength and may facilitate earlier ambulation.[134] Pertaining to the technique of performing popliteal block, studies have demonstrated higher sensory block success, reduced time to perform the block, reduced risk of vascular puncture, and requirement for less local anesthetic with ultrasonographic guidance versus peripheral nerve stimulation techniques.[139,140] When popliteal sciatic blockade is performed using ultrasonographic guidance, performing the block separately for the tibial and common peroneal nerves at the bifurcation may be associated with faster block onset and denser motor block compared to a prebifurcation popliteal sciatic blockade.[141,142]

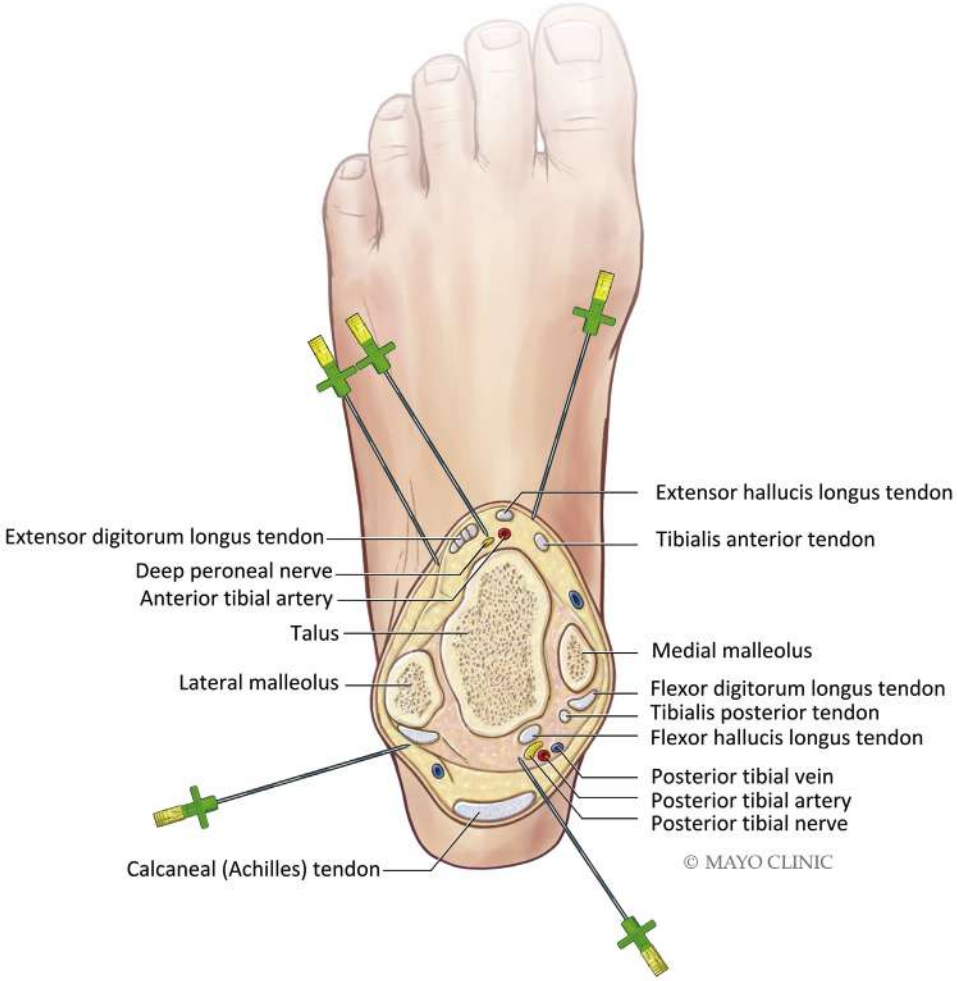
Popliteal sciatic nerve blockade provides excellent analgesia and surgical anesthesia for surgeries below the knee joint, notably foot and ankle surgery.[143,144] While an ankle block may be pursued for foot surgeries, a popliteal block is preferable when the surgery involves the use of a calf tourniquet. Supplementation with a saphenous nerve block is required for coverage of the medial aspect of the leg. Compared to single injection popliteal sciatic nerve blockade for foot and ankle surgery, continuous infusion of local anesthetic is associated with lower postoperative pain scores at 24 and 48 hours.[144] Although popliteal sciatic nerve blockade is primarily utilized for below the knee procedures, the combination of a popliteal sciatic nerve block and an adductor canal block may provide sufficient analgesia after TKA.[145] Furthermore, a combination of continuous popliteal sciatic and continuous femoral nerve block may improve postoperative pain control during movement following ankle surgery.[146]

Ankle Block

The ankle block involves injection at multiple sites around the ankle and foot to block several peripheral nerve targets (Fig. 26.4). These include derivatives from the sciatic nerve (deep fibular/



• **Figure 26.3** Popliteal Nerve. (Courtesy of Mayo Clinic.)



• **Figure 26.4** Ankle Block. (Henry Gray, Anatomy of the Human Body, 20e, Lea & Febiger, 1918.)

peroneal, superficial fibular/peroneal, sural, and posterior tibial nerves) and one derivative from the femoral nerve (saphenous nerve), which innervates the medial side of the ankle and foot.[147] This provides excellent surgical anesthesia and postoperative analgesia for surgeries of the foot, particularly surgeries not requiring calf tourniquet application. Since motor blockade is often unnecessary, high volumes of lower concentrations of local anesthetics may be administered to provide adequate sensory blockade; hence, the term "volume-block" is often used to describe the ankle block. Epinephrine is not recommended for use in ankle blocks, particularly if a circumferential infiltration technique around the ankle is used. The ankle block is ideal for ambulatory surgeries as patients may still ambulate with assistance, facilitating earlier discharge with adequate pain control.[148]

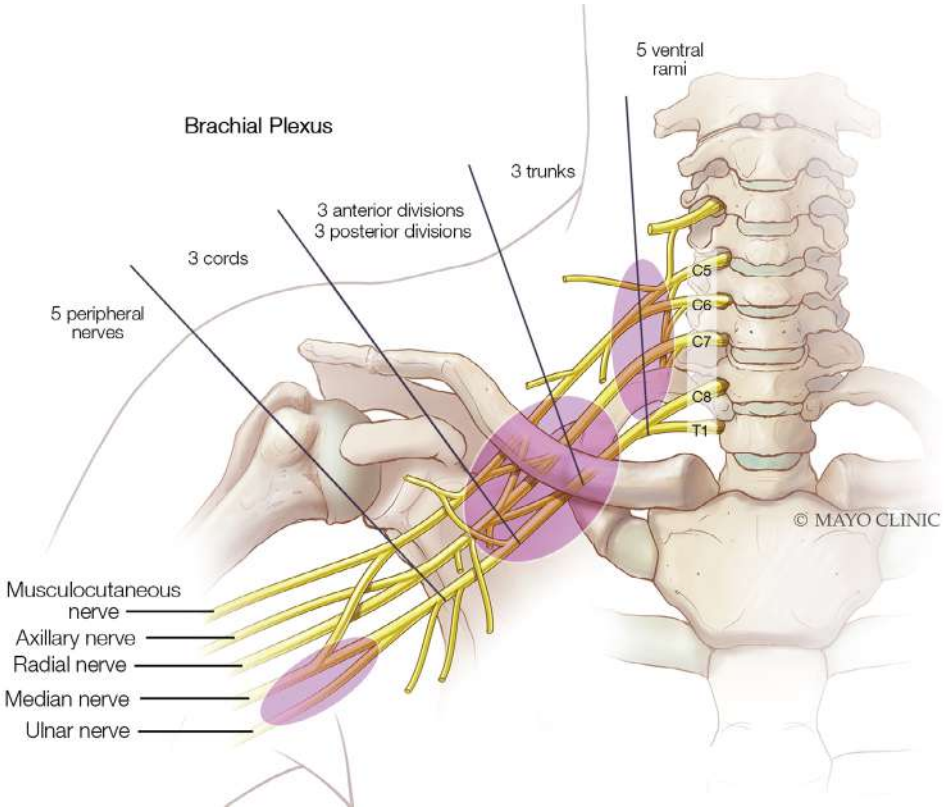
The ankle block may be performed using either a landmark-based approach or an ultrasound guided approach. Compared to the landmark approach, the use of an ultrasound for ankle block may be associated with a higher block success rate, although the lower local anesthetic volume in ultrasound guided injections may compromise postoperative analgesia in the first 24 hours.[148,149] In a study comparing spinal anesthesia and ankle block, ankle block was associated with lower pain scores and longer time to first need for analgesics but was associated with a longer time to sensory block.[150]

Upper Extremity Peripheral Nerve Blocks

The brachial plexus is formed by the anterior rami of the cervical nerves from C5–C8 and the first thoracic spinal nerve (T1) and provides motor and sensory innervation to the upper extremity. The brachial plexus consists of five roots, three trunks, six divisions, three cords, and five terminal branches (Fig. 26.5). The terminal branches include the radial, median, ulnar, musculocutaneous, and axillary nerves.[151] Depending on the nature and location of the upper extremity surgery, blockade of the brachial plexus can be targeted at any of these levels to provide surgical anesthesia and postoperative analgesia. Ultrasound allows reliable visualization of the brachial plexus. It may be associated with an increase in overall block success rate, quicker block performance time, use of less local anesthetic, faster onset of motor and sensory block, and minimal side effects when compared to traditional landmark-based and nerve stimulation techniques.[152–155]

Interscalene Block

An interscalene block is performed at the distal roots/proximal trunk level of the brachial plexus and provides excellent analgesia for shoulder and upper arm surgeries.[151] It is effective in providing a complete block of the superior and middle trunks, but coverage



• **Figure 26.5** Brachial Plexus. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

of the inferior trunk is frequently missed, thus making the interscalene block an unsuitable option for forearm and hand procedures that require ulnar nerve coverage.[156] If an interscalene block is performed for elbow procedures, additional supplemental nerve blocks may be required, including the intercostobrachial nerve block to cover the medial aspect of the arm, as well as the medial antebrachial cutaneous and ulnar nerve blocks to cover the medial aspect of the forearm. The spread of local anesthetic injectate in an interscalene block consistently spreads to cover the supraclavicular nerve (C3–4), which provides innervation to the cape of the shoulder.[157] If paresthesia or nerve stimulation technique is utilized, the desired response is preferably a paresthesia or motor twitch of the upper arm or hand. However, the stimulus of the deltoid/anterior shoulder may be acceptable.[158] If the contraction of the diaphragm is sometimes visualized as hiccups, this indicates phrenic nerve stimulation from a needle that is placed too anterior. If the needle is placed too posteriorly, stimulation of the dorsal scapular nerve may elicit rhomboid muscle movement.[159]

The interscalene block should be avoided in patients with impaired pulmonary function because the phrenic nerve is usually blocked using this technique.[160] The interscalene nerve block should not be performed in a patient under general anesthesia or deep sedation because of the risk of syrinx and other major neurological complications, including intrathecal and epidural injection.[161] Other potential complications from interscalene block include intravascular injection, particularly into the vertebral artery, pneumothorax, and Horner's syndrome.[160] Nerve injury may potentially occur in the dorsal scapular nerve, leading to a dull ache in the medial scapula and weakness of the rhomboid and levator scapulae muscles.[162] Nerve injury is also possible to the long thoracic nerve, resulting in chronic shoulder pain and serratus muscle weakness.[162–164]

A meta-analysis revealed that patients undergoing arthroscopic shoulder surgery who received an interscalene block with general anesthesia experienced lower pain scores up to one day postoperatively, lower intraoperative systolic blood pressure, shorter extubation time, and a lower rate of adverse events compared to general anesthesia alone.[165] Compared to systemic opioids, interscalene block is associated with superior analgesia, less postoperative opioid consumption, and less incidence of opioid-related side effects.[166] Patients may maintain the continuous perineural local anesthetic infusion via an interscalene catheter while at home with a portable infusion pump, allowing better pain control and improvement in rehabilitation indices with greater shoulder range of motion.[167,168] If there is concern for respiratory insufficiency in a patient undergoing shoulder surgery, an anterior suprascapular nerve block or a supraclavicular block approach may be pursued instead of an interscalene approach. However, even the more distal supraclavicular approach is associated with phrenic nerve blockade.[169] A meta-analysis of patients undergoing shoulder surgery revealed that patients receiving a supraclavicular block reported similar postoperative pain scores and postoperative opioid consumption but with lower rates of hemidiaphragmatic paresis and Horner's syndrome compared to those receiving an interscalene block.[170]

Supraclavicular Block

A supraclavicular block is commonly known as the "spinal of the arm" because the brachial plexus in this approach is tightly packed and can achieve quick, reliable, and dense blockade with little to

no sparing after local anesthetic infiltration.[171] The supraclavicular block is performed at the distal trunks/proximal cords level of the brachial plexus[172] and provides surgical anesthesia and postoperative analgesia for surgeries of the hand, forearm, and arm. While studies have shown that supraclavicular block may provide analgesia similar to that of an interscalene block,[170] other studies recommend supplementing the supraclavicular block with a separate superficial cervical plexus block of the supraclavicular nerve (C3–C4) to provide coverage of the shoulder cape.[151,173] In addition, supplementation with an intercostobrachial nerve block to provide coverage of the medial arm may be required for elbow surgeries or tourniquet application.

A feared complication from a supraclavicular block is pneumothorax, which may occur if the needle angle is aimed at the apex of the lung. The supraclavicular approach carries the highest risk for pneumothorax among all brachial plexus block techniques.[174,175] Phrenic nerve blockade occurs commonly, although not as common as in the interscalene approach, and thus may be avoided in those with impaired pulmonary function.[176] Hematoma may occur in the supraclavicular approach, commonly because of puncture of the subclavian artery.[177] Higher local anesthetic volumes should be avoided because ischemic compression within the tightly packed supraclavicular space is possible and may lead to indirect nerve injuries. Direct injury to the suprascapular nerve may also occur and manifests with shoulder pain and weakness of the supraspinatus and infraspinatus muscles.[178]

Although the supraclavicular block is considered to be the approach that provides the fastest and most reliable onset of dense blockade, RCTs have demonstrated that ultrasound guided brachial plexus blocks via the supraclavicular, infraclavicular, and axillary approaches all led to similar success rates, pain scores, and total anesthesia-related times.[179,180] Studies have also investigated the addition of dexmedetomidine adjuvant to supplement local anesthetic in supraclavicular blocks, demonstrating that it leads to improved analgesia with shorter onset time and longer duration compared to local anesthetic (ropivacaine) alone.[181] Furthermore, there was no difference in the rates of bradycardia or hypotension.[181] In terms of technique, UGRA and nerve stimulation techniques are considered superior to the blind technique because of a higher success rate and decreased rate of complications.[182]

Infraclavicular Block

The infraclavicular block is performed at the level of the brachial plexus cords, and either a single injection or continuous catheter infusion provides surgical anesthesia and postoperative analgesia for arm, elbow, forearm, and hand procedures.[151,183] The three cords (lateral, posterior, and medial) are named in relation to the axillary artery, but substantial variation in the true location of the cords in relation to the axillary artery may be present at the coracoid level.[184] Of all the brachial plexus block techniques, the infraclavicular approach likely allows for a more secure insertion site for catheters.[151] While there are three main approaches to the infraclavicular block described (coracoid, lateral sagittal, and vertical approach), the coracoid approach may be preferable to some because of the clear anatomic landmarks and the lateral entry point reducing the probability for pneumothorax and hemidiaphragmatic paresis.[185] However, the evidence on a preferred technique is limited, which is an area for future investigation.

Complications may include hematoma and vascular puncture, particularly of the axillary artery or vein, LAST potential, especially because of the need for a high volume of local anesthetic injectate, and sparing of the radial nerve distribution in the single injection technique.[186] Compared to the supraclavicular and interscalene approach, there is a lower incidence of pneumothorax or inadvertent neuraxial injection with the infraclavicular approach because it is more distant from the lung and neuraxis.[187] The infraclavicular block is also suitable for patients with pulmonary insufficiency, as phrenic nerve blockade is markedly reduced compared to supraclavicular and interscalene techniques.[188]

As aforementioned, an infraclavicular approach for arm surgeries provides equivalent regional anesthesia and analgesia compared to other brachial plexus blocks.[179,180] However, when comparing an infraclavicular continuous catheter infusion to a supraclavicular continuous catheter infusion, the former is associated with superior analgesia.[189] Compared to general anesthesia with volatile anesthetic for ambulatory hand and wrist surgery, infraclavicular nerve block as the primary anesthetic was associated with lower postoperative pain scores, decreased time to ambulation, and lower post-anesthesia care unit admissions.[190] Placement of an infraclavicular catheter with continuous local anesthetic infusion may result in less dynamic postoperative pain, reduced postoperative opioid requirements, and less sleep disturbance compared to placebo infusion.[191] Studies have also investigated the addition of dexmedetomidine adjuvant to supplement local anesthetic in infraclavicular blocks, demonstrating that it leads to increased duration of analgesia and enhancement of sensory and motor blockade, lower postoperative pain scores, and reduction in postoperative opioid requirements compared to local anesthetic (bupivacaine) alone.[192]

Axillary Block

The axillary block is performed at the level of the terminal nerves surrounding the axillary artery, consisting of the radial, ulnar, and median nerves. However, with ultrasound guidance, a more proximal cord/terminal nerve block is possible. The relationship of the musculocutaneous nerve deserves special attention with the axillary approach because it courses away from the axillary artery and is located in the belly of the coracobrachialis muscle.[193,194] Thus a separate injection into the coracobrachialis muscle or ultrasound guided perineural injection of the musculocutaneous nerve is warranted during an axillary block.[193,194] The axillary block provides surgical anesthesia and postoperative analgesia for hand and arm surgery and can be blocked through various techniques, including paresthesia, nerve stimulation, perivascular, trans-arterial, and ultrasound guided.[151,195,196] If an axillary block is utilized for primary surgical anesthesia, supplementation of the musculocutaneous, intercostobrachial, medial brachial cutaneous, and medial antebrachial cutaneous nerves are warranted to prevent tourniquet pain.

A review by Chin et al. demonstrated that the multiple injection technique for axillary block improved the block success rate, although the block time was longer than that with single- and double-injection techniques.[197] Compared to general anesthesia alone for ambulatory hand surgery, an axillary block for surgical anesthesia provides superior postoperative pain control, decreases postoperative opioid requirement, and increases the time to first analgesic medication request.[198,199] Potential complications include LAST, postoperative neuropathy, hematoma, and vascular puncture, particularly the axillary artery. Pulmonary complications are rare, and this block is preferable in patients with pulmonary insufficiency undergoing distal arm, forearm, and hand surgery.

Bier Block

Intravenous regional anesthesia, also known as the Bier block, provides surgical anesthesia and a bloodless surgical field for shorter duration distal extremity surgeries.[200] The Bier block may also be utilized to treat certain chronic pain conditions, including complex regional pain syndrome.[201] The mechanism of action involves the diffusion of local anesthetic from the veins to the nerves.[202] The local anesthetic of choice commonly used in Bier blocks is lidocaine. Long-acting local anesthetic agents, including bupivacaine, are not appropriate for Bier blocks.[203,204] It is recommended that the tourniquet remain inflated at least twice the systolic blood pressure for 30 minutes prior to deflation.[200,205] However, seizures have been reported even with a tourniquet time as long as 60 minutes with the use of the lowest effective dose of lidocaine.[206] In the event of Bier block failure, surgeon-administered infiltration of local anesthetic at the surgical site or conversion to general anesthesia may be performed.

The Bier block is relatively contraindicated in localized or systemic infections, peripheral vascular disease, sickle cell anemia, presence of arteriovenous fistulas, and lack of IV access. Side effects include phlebitis and LAST, which may be because of improper technique or tourniquet failure, nerve injury, compartment syndrome, and tourniquet pain. In addition to local anesthetic infusion, other studies have also evaluated other adjuvants to the Bier block, including opioids, steroids (e.g. dexamethasone, methylprednisolone), α-2-agonists (dexmedetomidine, clonidine), ketamine, and NSAIDs, notably ketorolac.[202,207,208] Of all opioids, some studies have described the efficacy of only meperidine,[209] while the remaining opioids are considered non-effective adjuvants.[204] Dexmedetomidine at a dose of 1 mcg/kg and clonidine at a dose of 1 mcg/kg may be associated with improved tourniquet tolerance and reduced postoperative analgesic requirements.[210] Furthermore, 100 mcg/kg of ketamine has been shown to also reduce postoperative analgesic requirements and improve tourniquet pain.[211] Up to 24 hours of reduced postoperative analgesic requirements may also be observed with a combination of dexamethasone and lidocaine versus plain lidocaine alone.[212]

Fascial Plane/Truncal Nerve Blocks

With the widespread use of ultrasonography, fascial plane blockade has been applied to various surgical procedures and acute pain management strategies.[213] A combination of systemic analgesic medications with truncal blocks of the abdomen, chest wall, or paraneuraxial nerves may offer similar analgesic efficacy and a lower risk profile when compared to neuraxial techniques.[214] The most common truncal blocks performed in the perioperative setting include the transversus abdominis plane (TAP), rectus sheath, ilioinguinal/iliohypogastric, intercostal, and paravertebral blocks. While most truncal blocks were initially described in the literature through landmark-based techniques,[215,216] the advent of ultrasonography has renewed interest in truncal blocks. It has improved the placement of local anesthetic in the appropriate location while avoiding injury to surrounding structures.[217] Unlike other peripheral nerve blocks, truncal nerve blocks are usually performed along muscular or fascial planes that spread to traversing nerves; thus visualization of the individual nerve or nerve plexus is not a requirement.[218]

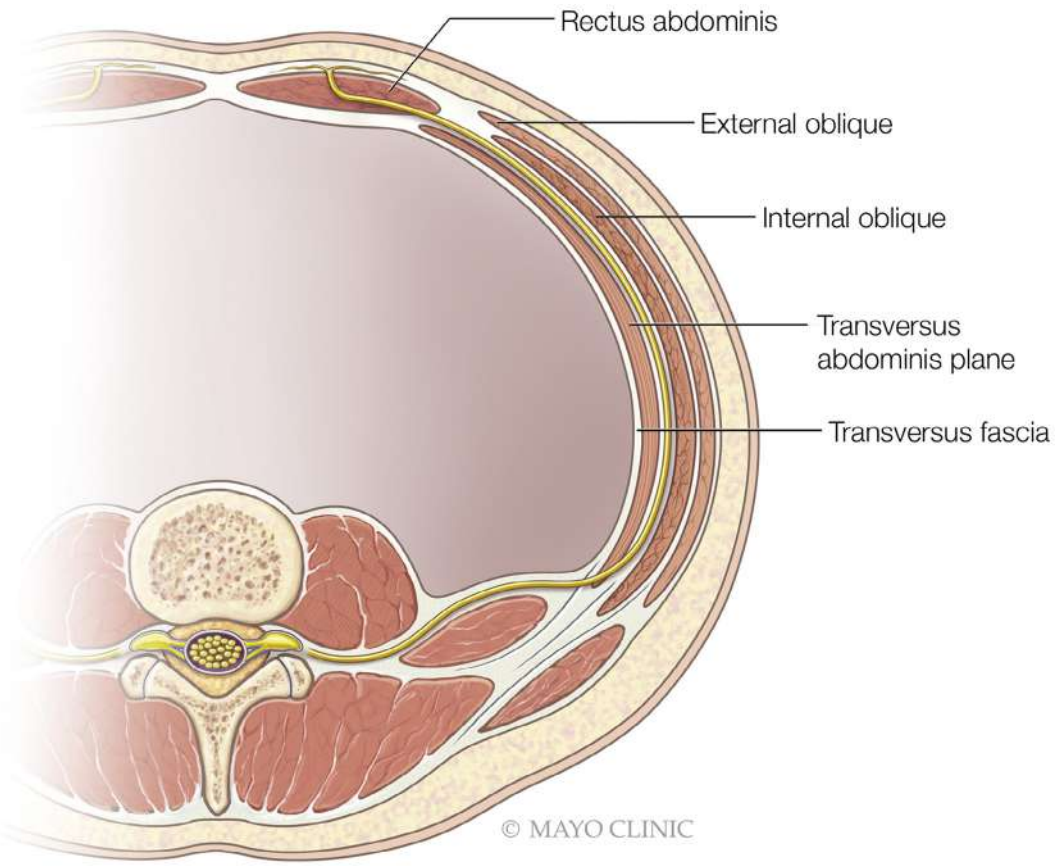
Transversus Abdominis Plane (TAP) Block

The (TAP) block has been used for postoperative analgesia after abdominal and gynecological surgeries, including hernia repairs, hysterectomies, appendectomy, and laparoscopic surgeries. The inclusion of TAP blocks in multimodal analgesia protocols is associated with a decrease in postoperative pain scores, opioid consumption, earlier ambulation, and shorter duration of hospital stay following laparoscopic cholecystectomy and appendectomy, as well as various laparotomy cases.[214,219–223] An RCT demonstrated that bilateral TAP blocks after abdominal hernia repair are associated with decreased time to ambulation and improved discharge readiness.[224] TAP blocks may obviate the need for neuraxial anesthesia and may be an option in the obese population, where neuraxial techniques may be challenging.[220] The TAP block covers nerves derived from the anterior rami of T7-L1 that provide sensation to the anterolateral abdominal wall skin, muscle, and parietal peritoneum (Fig. 26.6). Although statistically significant improvements in analgesia after TAP blocks for abdominal surgeries have been reported, these associations may only reflect a clinically modest benefit; thus this technique is not recommended for routine practice.[213] Furthermore, the TAP block may be limited in certain postsurgical settings, including coverage of midline incisional pain,[214] and presence of significant visceral pain,[225] and thus the implementation of a multimodal analgesia protocol is often necessary in these settings.

The TAP block should not be performed anteriorly in the abdominal wall because of concern for inadequate spread.[226] Furthermore, performing the block posterior to the midaxillary line has the advantage of targeting the lateral cutaneous branches prior to exiting the TAP.[227] Subcostal TAP blocks may provide analgesia for midline supraumbilical surgeries and upper abdominal incisions. The success of the block is dependent on the extensive spread of local anesthetic to traverse nerves across the abdominal wall; thus a high volume of dilute, long-acting local anesthetic (about 20 mL on each side) is preferred.[227,228] Adverse events may include damage to the viscera, retroperitoneal hematoma, nerve injury (e.g. femoral nerve palsy), and intravascular injection.[214] Caution is also advised when performing right-sided TAP blocks because of the proximity of the liver and the potential for liver injury in those with hepatomegaly.

Ilioinguinal and Iliohypogastric Nerve Block

The ilioinguinal and iliohypogastric nerve blocks provide postoperative analgesia following inguinal hernia repair, cesarean section, and other lower abdominal and inguinal surgeries. These nerves originate from the anterior ramus of the L1 nerve root and arise from the lateral border of the psoas muscle.[229] The iliohypogastric nerve travels superior to the ilioinguinal nerve and may give off lateral cutaneous branches that travel through the internal and external oblique muscles.[229] Thus these truncal nerves should be approached more proximally to avoid sparing of these lateral cutaneous branches.[229] The injectate is placed along the same plane as the TAP block (described above), although the optimal point of needle entry is 2.5 mm from the anterior superior iliac spine (ASIS) along a trajectory connecting the ASIS and the umbilicus.[214,230] Complications may include visceral damage, femoral nerve palsy, retroperitoneal hematoma, intravascular injection, and vascular injury, particularly of the inferior epigastric vessels that travel close to the ilioinguinal and iliohypogastric nerves.[214]



• **Figure 26.6** Abdominal Wall Innervation. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

In an RCT comparing a landmark-based technique versus ultrasound guidance for ilioinguinal/iliohypogastric nerve blocks in children undergoing unilateral inguinal surgery, use of ultrasound was associated with lower sevoflurane requirement intraoperatively, lower pain scores, decreased requirement for analgesics in the post-anesthesia care unit and increased parent satisfaction despite using a lower dose of local anesthetic to perform the block.[231] A meta-analysis comparing ilioinguinal/iliohypogastric nerve block versus TAP blocks for inguinal herniorrhaphy revealed that both techniques were associated with similar postoperative opioid consumption and patient satisfaction. In contrast, the ilioinguinal/iliohypogastric cohort reported better analgesic efficacy at 6 and 8 hours postoperatively compared to the TAP block cohort.[232] In patients with cervical cancer undergoing surgery, the addition of ilioinguinal/iliohypogastric blocks with general anesthesia compared to general anesthesia alone was associated with decreased intraoperative propofol and sufentanil requirements, decreased postoperative pain scores, and longer time until the administration of first postoperative analgesic medication.[233]

Rectus Sheath Block

The rectus sheath block provides postoperative analgesia for midline abdominal and periumbilical surgeries. The location of local anesthetic deposition is beneath the rectus abdominis muscle, which traverses the anterior intercostal nerves from T9 to T11.[234,235] Specifically, the needle tip should be between the rectus abdominis muscle and the double layer that is created by the transversalis fascia and aponeurosis of the transversus abdominis muscle.[236] It is important to note that above the arcuate line, both the aponeurosis of the transversus abdominis muscle and the transversalis fascia separates the rectus abdominis from the abdominal cavity. However, caudal to the arcuate line, the rectus abdominis muscle is only separated from the abdominal cavity by the transversalis fascia.[237] Furthermore, rectus sheath blocks would only provide coverage for midline abdominal surgeries, and the presence of lateral incisions would need to be supplemented with a TAP block (discussed above). Similar to the TAP block, the rectus abdominis sheath block does not provide analgesia for visceral pain. The use of ultrasound is recommended as one study demonstrated that 21% of rectus sheath blocks performed using a landmark-based loss-of-resistance approach led to intraperitoneal needle entry.[238] Other risks include infection, post-procedural pain, LAST, visceral organ damage, and intravascular injection, particularly in superior or inferior epigastric vessels.[213,239]

Compared to patients undergoing abdominal surgeries who did not receive any block or received a sham block, those who received preoperative rectus sheath blocks generally had lower intraoperative anesthetic requirements, decreased postoperative analgesic requirement and opioid consumption, and decreased postoperative pain scores.[240,241] Furthermore, the combination of the TAP block and rectus sheath block may improve postoperative pain, reduce analgesic requirements, and accelerate postoperative recovery after major abdominal surgeries.[242] In certain high-risk patients with limited cardiovascular reserve, case reports of using

rectus sheath blocks as the primary surgical anesthetic for standard periumbilical surgery have been reported.[236]

Thoracic Paravertebral Block

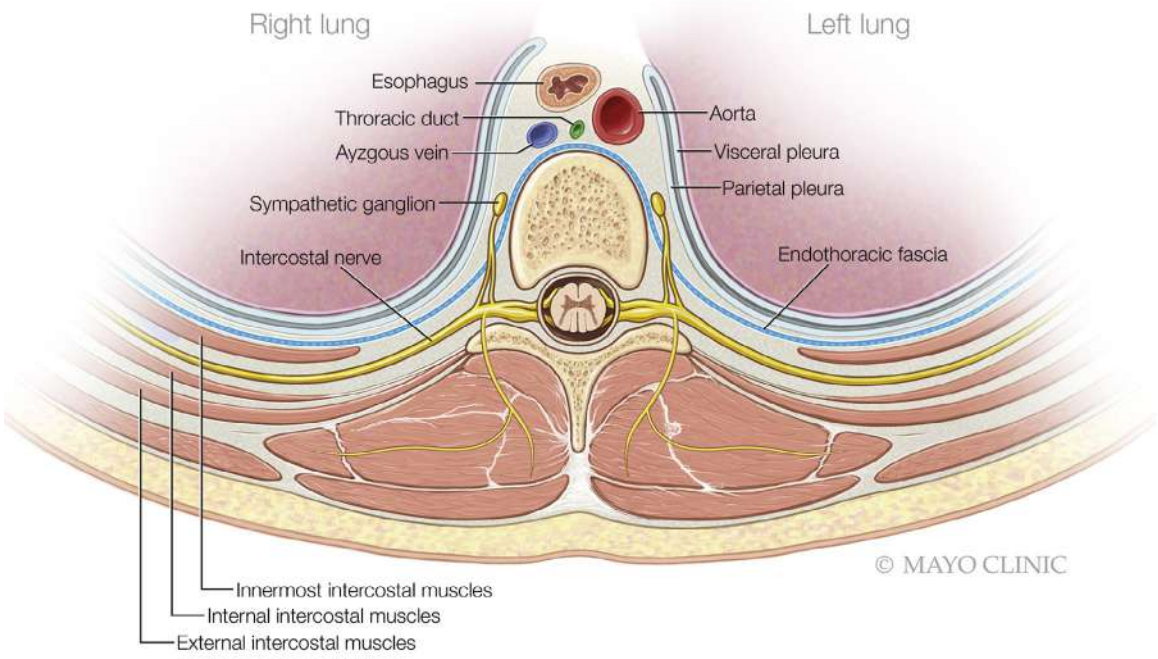
The thoracic paravertebral block provides postoperative analgesia for cardiac and thoracic procedures, including thoracotomy, nephrectomy, rib fractures, chest tube insertion, and breast surgeries. Bilateral thoracic paravertebral continuous catheters are particularly useful when the placement of an epidural catheter is difficult or not pursued. A thoracic paravertebral block may also be performed in the chronic pain setting in cases of complex regional pain syndrome.[243] The proposed mechanism of the thoracic paravertebral block is the direct spread of local anesthetic into the spinal nerves, lateral tracking of local anesthetic toward intercostal nerves, and medial tracking of local anesthetic into the intervertebral foramina (Fig. 26.7).[244] Several factors may impact the efficacy of the paravertebral block. However, a successful block is usually correlated with inferior needle advancement to the transverse process, medially directed bevel, large-volume and higher speed of injection to overcome negative intrathoracic pressures, absence of surgical emphysema from subcutaneous air, absence of fracture or blood in the intercostal space, and absence of anatomical abnormalities such as foraminal stenosis, disc herniation, and facet joint hypertrophy.[244–246] Adverse effects may include procedural pain, LAST because of large volumes, nerve injury, pneumothorax, hypotension from neuraxial spread, potential for total spinal blockade, and potential for quadriceps muscle weakness if the block is inadvertently placed below L1 with resultant femoral nerve blockade.[244,247]

While the efficacy of analgesia from a paravertebral block may be similar to that of an epidural block, the paravertebral block may allow for a more targeted coverage (e.g. unilateral block), less sympathectomy, lower rates of failed block, and lower rates of side effects including urinary retention, nausea and vomiting, and hypotension.[244,248,249] Furthermore, continuous paravertebral anesthetic infusions are associated with superior postoperative analgesia, greater preservation of lung function, and fewer side effects than interpleural analgesia for thoracic surgery.[250,251]

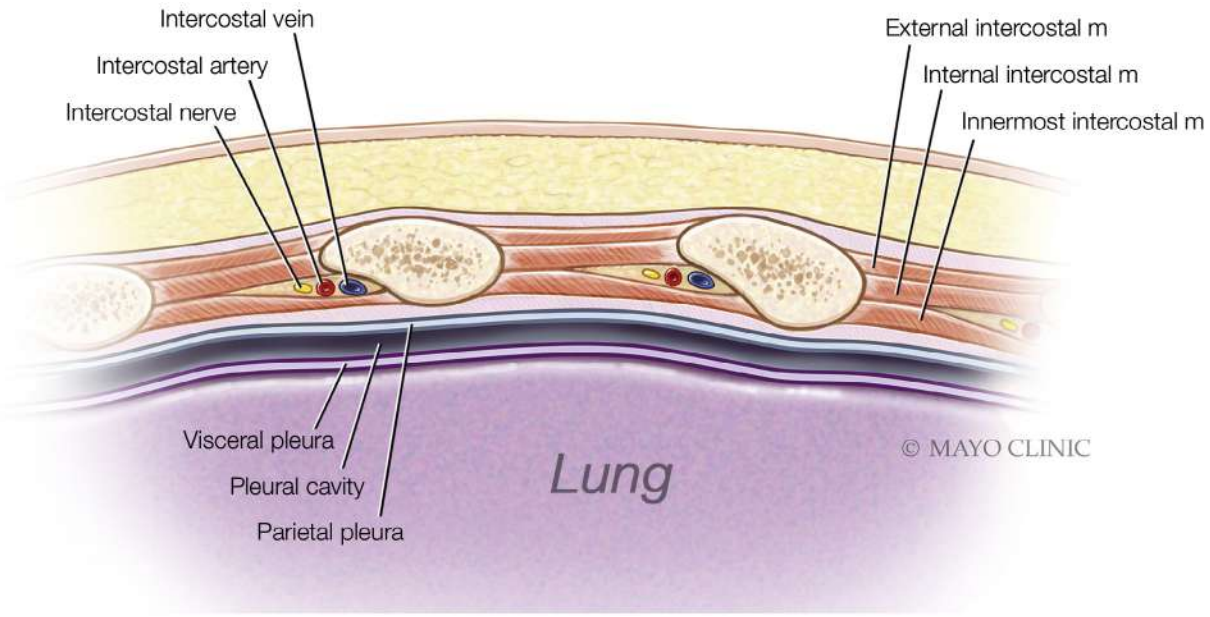
Intercostal Nerve Block

The intercostal nerve block provides postoperative analgesia for upper abdominal and thoracic surgeries and surgical anesthesia for minor surgical chest or abdominal procedures (Fig. 26.8).[252,253] Intercostal nerve blocks may also provide analgesia for rib fractures, chest tube placements, and gastrostomy tube placements.[254] The mechanism of action is the direct local anesthetic effect on intercostal nerves. However, if a catheter is inserted medially at the angle of the rib and if the catheter lies medially to the border of the intercostalis intimus muscle, local anesthetic may spread to the paravertebral space.[255] Above the T7 level, an intercostal nerve block may be technically challenging to perform because of the scapula; thus if analgesia is desired above T7, alternative modalities such as a paravertebral block or epidural catheter should be pursued.

Because of the significant vascularity within the intercostal space, systemic concentrations of local anesthetic are high following intercostal nerve blocks, and caution must be exercised when performing multiple-level intercostal nerve blocks.[256] Furthermore, peak serum local anesthetic concentrations may not be reached until 15–20 minutes post-procedure, and thus the patient should be monitored for LAST during this interval.[256] Although rare, pneumothorax is a serious potential complication after intercostal block, with an overall incidence of 8.7% per patient and 1.4% per intercostal nerve block.[257]



• **Figure 26.7** Paravertebral Space Anatomy. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.



• **Figure 26.8** Intercostal Nerve. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

An RCT in patients undergoing video-assisted thoracoscopic surgery reported that the addition of an intercostal nerve block was associated with better postoperative analgesia and less morphine consumption in the early postoperative period (6 hours) compared to those who did not receive an intercostal nerve block.[258] This is consistent with another study reporting improved postoperative analgesia and quality of life after patients received intercostal nerve blockade for percutaneous nephrolithotomy.[253]

Erector Spinae Plane Block

The erector spinae plane block (ESPB) is a relatively novel interfascial plane block initially described in the setting of chronic thoracic neuropathic pain and video-assisted thoracoscopic surgery.[259] The deep needle approach to ESPB, which is the recommended approach, involves local anesthetic injection deep to the three erector spinae muscles (iliocostalis, longissimus, and spinalis) but superficial to the thoracic transverse processes.[259] The superficial approach involves local anesthetic injection between the erector spinae muscle and the rhomboid major muscle.[260] When utilizing the deep approach, studies have demonstrated injectate spread from C7 to T8 on the right side and T1 to T8 on the left side within the paraspinous gutter and lateral spread toward the transverse processes.[259,261] Owing to its relative distance from the pleura, major blood vessels, and spinal cord compared to the paravertebral block, the ESPB provides a favorable adverse risk profile. Furthermore, unlike neuraxial analgesia, ESPB may be performed in patients with thoracic vertebral fractures.[262]

ESPB has been described as an effective analgesic modality for rib fractures as well as a variety of surgeries, including thoracic surgery (e.g. video-assisted thoracoscopy, thoracotomy), cardiovascular surgery (e.g. aortic valve replacement), breast and thoracic mass surgery, open abdominal and laparoscopic surgery, and spinal surgery. Given the novelty of this fascial plane block, most of the evidence for its use in postoperative analgesia consists of case reports and small retrospective studies. A cohort study in patients with traumatic rib fractures who received ESPB showed significant improvement in incentive spirometry and reduction in pain scores with no hemodynamic instability. While there was a reduction in opioid intake, this did not reach statistical significance.[263]

Although complications specific to the ESPB are rare, there have been reported cases of pneumothorax,[264] bilateral lower extremity weakness,[265] and LAST with central nervous system effects.[266] It is recommended that those receiving an ESPB at the lower thoracic or lumbar levels be evaluated for motor weakness after completion of the block.[267] The potential for block failure or lack of analgesic efficacy has been reported in several studies, although risk factors have yet to be identified.[266,268] Future studies are warranted to characterize differences in the ESPB approach (superficial vs. deep technique), optimal volume and concentration of local anesthetic, timing of block, respiratory function, and efficacy of unilateral and bilateral ESPB for various surgical indications.

Modes of Local Anesthetic Delivery

There are many variations in the delivery of local anesthetic to the block target site. The most basic is the single injection of local anesthetic, which is commonly performed for intrathecal analgesia and various peripheral nerve blocks. Single injection blocks are performed for ambulatory and short-duration procedures and typically provide short-term surgical anesthesia and analgesia depending on the local anesthetic medication injected. For instance, a single injection of peripheral nerve block with bupivacaine provides longer postoperative analgesia than intermediate-acting agents such as lidocaine.

If a catheter is placed for continuous infusion of local anesthesia, different delivery settings, including continuous infusion, intermittent bolus dosing, or a combination of both, may be pursued. Intermittent bolus dosing may be categorized as either manually delivered intermittent bolus dosing or programmable intermittent bolus dosing. Studies have examined PCEA, which provides excellent analgesia for various surgeries and is

associated with few complications.[269] While many RCTs have compared intermittent bolus dosing and continuous infusion delivery modes, a recent systematic review demonstrated limited evidence and reported no differences between intermittent bolus dosing over continuous infusion modes in truncal and peripheral nerve blocks.[270] For certain ambulatory surgeries, the patient may be discharged home with a perineural catheter in place and an ongoing continuous local anesthetic infusion for prolonged postoperative analgesia.[75,271] If the patient is discharged with a continuous perineural local anesthetic infusion, it is important to educate the patient on potential risks, potential for LAST, signs of infection and bleeding, and vigilance for other concerns. Suppose the patient manifests any signs or symptoms of LAST or other adverse events from regional anesthesia. In that case, the patient should stop the local anesthetic infusion, contact the acute pain service (if available at their hospital), and consider transport to the emergency department for further evaluation.

Special Patient Populations

Obese Patients

Obesity may present unique challenges in terms of perioperative analgesia. A significant proportion of obese patients have obstructive sleep apnea (OSA) and, vice versa, up to 90% of OSA patients may have obesity.[272] Thus pain management plans for patients with severe obesity, morbid obesity, or OSA include a multimodal analgesia approach that avoids or limits sedating medications and systemic opioids and utilizes regional anesthesia modalities.[273,274] This is consistent with the guidelines from the ASA Task Force on perioperative management of OSA patients.[275] A study by Batistich and colleagues demonstrated that administration of regional anesthesia and systemic non-opioid analgesia to morbidly obese patients undergoing bariatric surgery decreased the requirement for systemic opioids.[276] If sedative medications and systemic opioids are administered, obese patients and patients with OSA should be monitored for respiratory depression during the first 24 hours postoperatively, and providers should consider instituting continuous and/or remote pulse oximetry.[275,277] Furthermore, regional anesthesia may be more technically challenging and associated with block failure in obese patients. Nielsen et al. demonstrated that obese patients were 1.62 times more likely than non-obese patients to experience block failure.[278] Finally, the regional anesthesiologist must consider the elevated risk for anticoagulation needs in the obese population postoperatively.[279] Refer to the section below regarding "Patients on Anticoagulation."

Patients with Pulmonary Disease

Patients with pulmonary disease and respiratory insufficiency may benefit from utilizing regional anesthesia and avoiding sedative medications and general anesthesia.[280] However, the adverse effect profile of certain regional techniques may be detrimental to a patient with existing pulmonary disease and merits discussion. Ipsilateral phrenic nerve palsy is a common complication in brachial plexus blocks and almost always occurs in interscalene blocks.[281,282] While healthy patients may compensate for the decrease in pulmonary function, patients with cardiopulmonary disorders and moderate to severe respiratory dysfunction (e.g. severe chronic obstructive pulmonary disease, preexisting contralateral phrenic nerve palsy) may not tolerate the reduction in pulmonary function from ipsilateral phrenic nerve blockade.[281,283] Although ultrasonography, low-volume local anesthetic infiltration, and digital pressure above the injection site have been implemented, these techniques have not been associated with reduced phrenic nerve palsy.[281,284] Alternative peripheral nerve blocks may be utilized, including direct local anesthetic infiltration at the surgical site, Bier block, infraclavicular block, and axillary block, all of which carry a much lower risk for phrenic nerve palsy.[281,285]

In terms of neuraxial blockade, the presence of a high spinal or epidural anesthesia may decrease expiratory reserve volume and vital capacity and reduce the ability to forcefully exhale, cough, or clear pulmonary secretions.[286] This is usually because of paralysis of the abdominal muscles.[286] A study in elderly patients with poor respiratory reserve who received spinal anesthesia with a level above T6 demonstrated significant decreases in forced expiratory volume in one second (FEV1), forced vital capacity, and forced expiratory flow 25%–75%.[287] Tidal volume is typically not impacted unless the phrenic nerve (C3–5) is affected by higher neuraxial blockade.[286]

Trauma and Critically Ill Patients

Trauma and critically ill patients experience an amplified inflammatory response, which may activate peripheral nociceptors and initiate neurogenic inflammation that increases the release of certain nociceptive neurotransmitters such as substance P and calcitonin gene-related peptide.[288] Undertreatment of pain in trauma and critically ill patients is a major concern. It may be attributed to the inability to perform a proper pain assessment, concern for unstable hemodynamics, fear of sedation and analgesia masking and interfering with the diagnosis of underlying injuries, the misconception that sleep implies lack of pain, concern for addiction, and the misconception that trauma patients do not recall painful episodes.[289–291] After establishing stable hemodynamics, cautious analgesic administration is indicated and may even make the patient more cooperative after adequate pain control is achieved, permitting further assessment and detection of unrecognized injuries. This may be especially critical in assessing cervical spine injuries because distracting injuries may interfere with accurate diagnosis.[292]

Peripheral nerve blockade and neuraxial techniques play an important role and may reduce the need for opioids and other sedative agents. Various regional anesthesia techniques may offer significant analgesia depending on the location of the injury. Brachial plexus blocks, lower extremity blocks, and neuraxial blocks may provide analgesia to the upper extremity, lower extremity, and thoracic/truncal injuries, respectively. With rib fractures, neuraxial analgesia, paravertebral blocks, ESPB, and intercostal blocks offer significant analgesia, decrease the need for opioids, and may be associated with improved respiratory indices by preventing splinting (improved oxygenation, tidal volume, and inspiratory force; decreased atelectasis and ventilation/perfusion mismatch).[293–295]

If neuraxial blockade is pursued, the proceduralist should ensure definitive spinal cord injury clearance. Furthermore, in patients with head trauma and the potential for elevated intracranial pressure, neuraxial techniques may not be an option because of the potential for herniation of the brain and cerebral structures as well as expansion of intracranial hematomas.[296] Additionally, coagulopathy is common in patients with polytrauma, which would be a contraindication to neuraxial analgesia. It is also recommended

that certain peripheral nerve blocks performed close to the neuraxis (e.g. lumbar plexus block, paravertebral blocks) and at non-compressible sites (e.g. infraclavicular nerve block) be avoided in polytrauma cases with coagulopathy. Finally, hemorrhagic shock and hemodynamic instability are commonly present in trauma patients, leading to ischemia and multiple-organ dysfunction.[297] Ketamine and various non-opioid analgesics have been shown to provide effective analgesia with limited effects on hemodynamics.[298] Furthermore, sympathectomy from neuraxial local anesthetics may be undesirable in trauma patients with hemodynamic instability; in such cases, opioid-only infusions may be utilized with a better hemodynamic profile.

Patients on Anticoagulation

The incidence of bleeding complications from neuraxial blocks is unknown, but some sources cite an incidence of one in 150,000 epidural blocks and one in 220,000 spinal blocks.[299] This risk is elevated in certain populations, such as those taking anticoagulants and those with coagulopathy disorders. Guidelines on performing regional anesthetic techniques are based on guidelines derived from a retrospective analysis of observational data and pharmacologic dosing studies.[299] There are no laboratory models available, and prospective randomized studies are not possible because of ethical reasons and the requirement for very large sample sizes. Finally, this issue is further compounded by medication-related factors (duration of therapy, degree of anticoagulation), procedure-related factors (location of regional block, need for catheter placement), patient-specific factors (obesity, advanced age, personal or family history of coagulopathy, trauma, pregnancy), surgery-related factors, and other pharmacologic factors (concomitant use of herbal medications that increase the risk of bleeding, polypharmacy, and drug-drug interactions), all of which may impact bleeding risk.[299]

As previously mentioned, certain regional techniques are less suitable for patients with potential coagulopathy and increased risk for bleeding, including neuraxial analgesia, nerve blocks performed close to the neuraxis (e.g. lumbar plexus block, paravertebral blocks), and peripheral nerve blocks performed at non-compressible sites (e.g. infraclavicular nerve block). The proceduralist should also refer to recommendations and guidelines published by reputable societies such as the American Society of Regional Anesthesia (ASRA) and the European Society of Regional Anesthesia (ESRA) regarding discontinuation of anticoagulation perioperatively and for high-risk regional anesthetic procedures.[300,301] Variations between the two practice recommendations have been narrowed as members of the ESRA anticoagulation Writing Committee helped formulate the latest edition of the ASRA guidelines.[300,301]

A thorough risk-benefit analysis of performing regional anesthesia in anti-coagulated patients is warranted and should be individualized. Further details on the implications of anticoagulation from common pain related procedures are included in Chapter 74.

Conclusion

With the increased implementation of ERAS and multimodal analgesia pathways in the perioperative setting, studies continue to show improvements in patient-reported pain scores, improvements in rehabilitation, and decreased hospital stays. Acute pain proceduralists should consider for each patient a unique and individualized treatment plan while taking into account the nature of the surgery, anatomic location, procedural factors, expected hospital duration, and side effect profile. Unless contraindicated, multimodal pathways should always include NSAIDs or acetaminophen and utilize regional anesthetic techniques.

Key Points

- While opioids remain the mainstay of postoperative analgesia for moderate to severe pain, multimodal analgesia is recommended and includes other non-opioid analgesics with different mechanisms of action.
- Neuraxial analgesia provides superior pain control over systemic opioids for various abdominal, thoracic, and lower extremity surgeries. This route of analgesia is not suitable in certain scenarios, including therapeutic anti-coagulation, bleeding disorders, certain neuroanatomic abnormalities, elevated intracranial pressure, and intracranial hematoma.
- Lumbar plexus blocks provide analgesia for hip and knee procedures, while the psoas compartment block is considered an advanced regional anesthetic block because of its proximity to the neuraxis as well as its non-compressible location.
- Sciatic nerve blockade may be performed through various approaches, including parasacral, subgluteal, and popliteal, as well as surgical anesthesia and postoperative analgesia for TKA and below the knee surgeries.
- The interscalene brachial plexus block provides analgesia for shoulder surgeries, supraclavicular block provides analgesia for upper arm and elbow surgeries, while both infraclavicular and axillary blocks provide analgesia for elbow, forearm, and hand surgeries.
- Depending on the approach to brachial plexus blockade, sparing of various nerves may occur, including the ulnar nerve (interscalene block), musculocutaneous nerve (axillary block), and intercostobrachial nerve (spared in all brachial plexus blocks).
- The transversus abdominus plane, rectus abdominus, and ilioinguinal/iliohypogastric nerve blocks provide somatic pain coverage of the abdominal wall but do not provide visceral pain coverage.
- Neuraxial analgesia, paravertebral blocks, and intercostal blocks may provide analgesia for breast, thoracic, cardiac, and upper abdominal surgeries, although more side effects are associated with neuraxial techniques.
- Administration of opioid analgesics and regional anesthesia warrants special consideration of the adverse effect profile in certain at-risk populations, including obese patients, patients with OSA, trauma and critically ill patients, patients with pulmonary disease, patients with bleeding disorders, or those taking anticoagulant medications.

Acknowledgments

The authors acknowledge that some of this chapter's information has been modified from previous editions of *Practical Management of Pain*, including "Postoperative Pain and Other Acute Pain Syndromes" authored by Drs. Marie N. Hanna, Jean-Pierre P. Ouanes, and Vicente Garcia Tomas.

Suggested Readings

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27

Evaluation and Treatment of Postoperative Pain in Patients With Opioid Use Disorder

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Background

Because of the dramatic increase in the number of opioid related deaths since 1999, the opioid epidemic was declared a "public health emergency" in the United States on October 26, 2017.[1] The opioid abuse epidemic arose in part from a lack of acknowledgment about the high addiction potential of opioids along with aggressive widespread pharmaceutical company marketing of prescription opioids for both acute and chronic pain treatment in the late 1990s.[2,3] This led to pervasive opioid diversion, opioid abuse, and a rapid rise in opioid overdoses, leading to over 47,000 people in the United States dying from an opioid overdose in 2017.[4] As seen in Fig. 27.1, from 2010–2015 the annual number of deaths from prescription opioids remained relatively stable. However, overdose deaths from illicit opioids (heroin followed by high-potency synthetic opioids such as fentanyl) nearly tripled. This large increase in illicit opioid use was driven in part by people prescribed opioids and who subsequently developed opioid use disorder (OUD).[5,6]

OUD is defined by the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition, criteria as having at least two of the criteria illustrated in Table 27.1. As of 2015, two million Americans aged 12 years or older had an OUD involving prescription opioids, and nearly 600,000 had an OUD involving heroin. Opioid-attributable deaths increased 292% between 2001 and 2016.[7] In 2016, the approximate person-years of lives lost in the United States from opioid-attributable deaths was 1.68 million (5.2 per 1000 population),[7] and opioid overdose was linked to an average of two-thirds of the 175 daily deaths related to all drug overdoses in the United States.[8] The economic burden of prescription opioid abuse in 2013 was estimated to be almost $80 billion.[9] The global burden of disease from opioid related conditions approaches 11 million life-years lost from health problems, disabilities, and early death.[10]

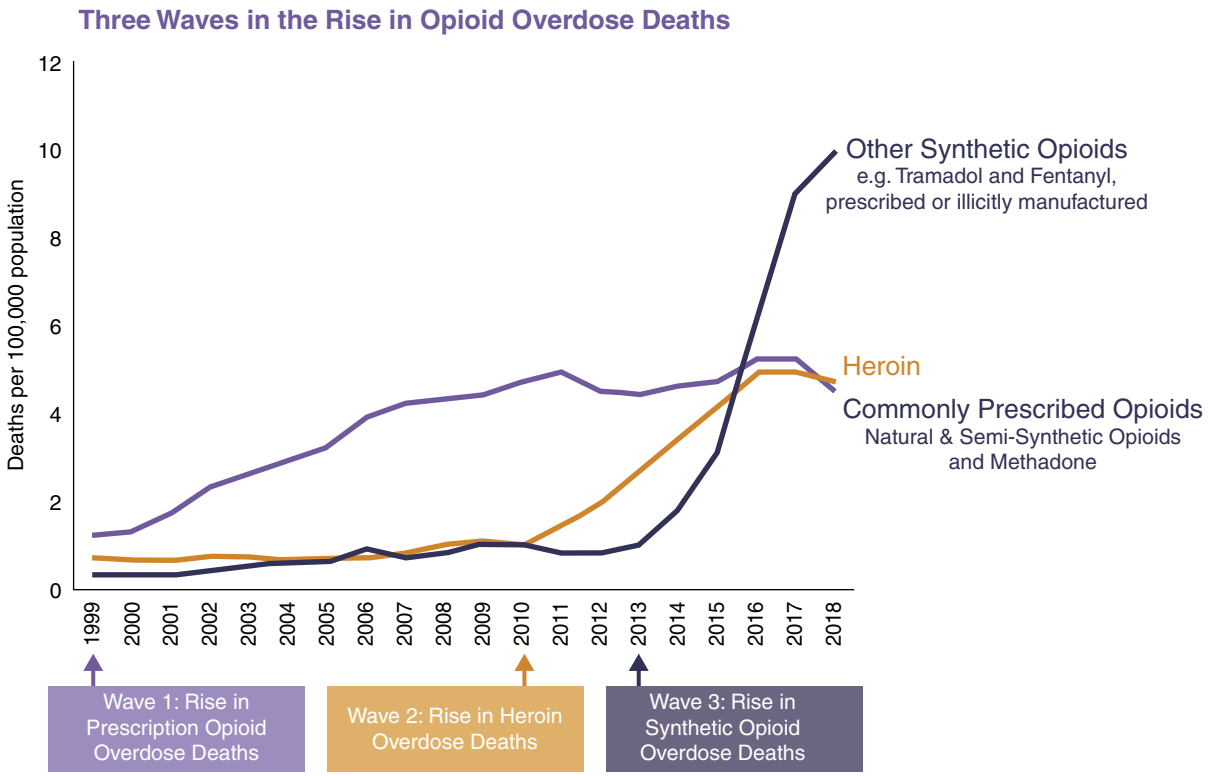
Some patients are at a higher risk of developing OUD, and widely available scoring systems such as the opioid risk tool (ORT) were developed to screen for the likelihood of aberrant behavior. These criteria included a personal history or family history of illicit substance use, comorbid psychological disorder, age between 16 and 45 years, and history of preadolescent sexual abuse (Table 27.2).[11] One study found that patients who were younger, had comorbid depression, used psychotropic medications, and were impaired by pain had a significantly increased risk of developing OUD (odds ratio of eight).[6]

Comorbid chronic pain (CP) and substance use disorders (SUD) are very common. Chronic non-cancer pain (CNCP) is common among patients treated for SUD, and SUD is common among those treated for CNCP. The lifetime prevalence of CP in patients with SUD is over 50% and as high as 75% in those actively treated for SUD. The overall prevalence of current SUD among patients with CNCP is as high as 48%, and the lifetime prevalence of any SUD in those CNCP is as high as 74%.[12–14] SUD may result from substances used to cope with pain symptoms, and/or substance use-related injury may lead to CP conditions.[15,16] However, many experts now believe that a diathesis-stress model best explains these comorbidities. Patients have preexisting, semi-dormant characteristics of the individual before the onset of CP, which are then activated and exacerbated by the stress of this chronic condition, eventually resulting in diagnosable psychopathology.[17] Several studies have examined the chronologic relationship between CNCP and SUD with conflicting evidence.[18–21]

The management of pain in patients with SUD, specifically OUD, has not been investigated in detail. Studies published on the co-management of OUD and CNCP suggest the use of 1) multi-disciplinary care teams, 2) stepped care models, and 3) multimodal treatments with a combination of nonpharmacologic, non-opioid pharmacologic, and buprenorphine or methadone.[22–25] In 2012, the Center for Substance Abuse Treatment published a thorough set of recommendations for managing CP in patients with SUD based on expert recommendations.[26]

It is critical to understand that the risk of death in adults with SUD is significantly higher than in those without; even patients undergoing SUD treatment have a mortality rate approximately four times that of the general United States population,[27] while those with OUD also have a significantly elevated mortality rate.[28] Even those with OUD and treated with an opioid agonist have a significantly higher death rate from drug abuse and other causes than the general population.[29] Thus in those patients being actively treated for OUD, relapse may be lethal. Clinicians must be aware that pain management in patients with active addiction or in treatment, especially treatment involving opioids, is perilous.

This chapter will review the latest evidence for the management of acute postoperative pain in patients with comorbid OUD.



SOURCE: National Vital Statistics System Mortality File.

• **Figure 27.1** The three waves of the rise of opioid overdose deaths with Wave 1 because of a rise in prescription opioids, Wave 2 because of illicit drugs such as heroin, and Wave 3 because of synthetic opioid usage, such as fentanyl. Image available at: https://www.cdc.gov/drugoverdose/epidemic/index.html.

TABLE 27.1 DSM-V Criteria for Opioid Use Disorder

Opioids are often taken in larger amounts or over a longer period than was intended.
There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
Craving, or a strong desire or urge to use opioids.
Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
Important social, occupational, or recreational activities are given up or reduced because of opioid use.
Recurrent opioid use in situations in which it is physically hazardous.
Continued opioid use despite having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance.
Exhibits tolerance.*
Exhibits withdrawal.*

*This criterion is not considered for those taking opioids solely under appropriate medical supervision. At least two of the criteria should be observed within 12 months. If two or three Items cluster together in the same 12 months, the disorder is mild; if four or five items cluster, the disorder is moderate; and if six or more items cluster, the disorder is severe. These criteria are from the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition.[195]

Given the paucity of published evidence on this topic, recommendations from experts in the field and data from the management of perioperative pain alone are extrapolated to the care of patients with comorbid SUD.

Management of Opioid Use Disorder

The Substance Abuse and Mental Health Services Administration (SAMHSA) has determined that the combination of medication assisted treatment (MAT) and cognitive behavior therapy should be used to manage patients with OUD.[30] The three medications approved by the United States Food and Drug Administration for MAT are methadone, buprenorphine, or naltrexone.

The outcomes of MAT treatment in patients with OUD are dramatic; patients who use methadone have retention rates of 60%–84%,[31,32] and patients who use buprenorphine have similar results.[33,34] Importantly, mortality rates also decrease with the use of these medications. In a well-cited randomized placebo control trial comparing buprenorphine to a placebo, the

TABLE 27.2 The Opioid Risk Tool

Family History of Substance Abuse	Female	Male
Alcohol	1	3
Illegal drugs	2	3
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Prescription drugs	5	5
Age between 16-45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar schizophrenia	2	2
Depression	1	1
Total score		

Opioid risk tool may be used to screen patients and indicates the risk of opioid use. A ccore of zero to three indicates low risk, a score of four to seven indicates moderate risk, and a score higher than eight indicates high risk. Adapted from Webster and Webster 2015.[11]

placebo group dropout rate was 100% by the second month, with all subjects demonstrating urine samples positive for drug use and mortality rate of 20%.[32] Buprenorphine-treated patients demonstrated a 75% retention rate and a mortality of 0% at one year.[33] A meta-analysis assessing methadone versus buprenorphine treatment for patients with OUD found that subjects who received 8–12 mg/day buprenorphine had 1.26 times the relative risk of discontinuing treatment and 8.3% more positive urinalyses than subjects receiving 50–80 mg/day methadone.[34] However, different dropout rates have been observed with other doses of methadone. For example, patients who receive doses of less than 60 mg of methadone are significantly more likely to drop off treatment than those who received doses of 80 mg or more.[35]

Acute Pain Treatment Goals

The appropriate management of new-onset pain in patients with OUD depends on the origin of pain (i.e. new postoperative acute pain versus acute on chronic exacerbation). As recommended above, management should include a multispecialty approach and multimodal pharmacologic and nonpharmacologic treatments. The goals of treating acute pain in patients with OUD are to prevent withdrawal, provide adequate analgesia, and avoid triggering a relapse if a patient is in recovery (or worsening of the disorder if a patient has active addiction).

The most common causes of acute pain include surgery, fracture, dental work, cuts, and burns. Patients taking opioids to control CP, OUD, or illegitimately should not be intentionally weaned off opioids during an acute pain episode because of the risk of withdrawal and presumed hyperalgesia. A multimodal regimen, including nonpharmacologic therapies, regional anesthesia, and/or non-opioid medications, may reduce the need for additional opioid medications.[36] Continuous regional anesthesia provides superior perioperative analgesia compared to opioid-based management of acute pain and should be strongly considered when possible as part of the multimodal pain management plan for patients who undergo surgery.

Challenges of Postoperative Pain Management in Patients With Opioid Use Disorder

There are many challenges in treating acute pain in patients with OUD, including withdrawal, tolerance, hyperalgesia because of chronic opioid exposure, and comorbid psychological conditions, including the risk of relapse.

Withdrawal. Withdrawal during hospitalization can occur after underdosing inpatient opioids and/or sudden discontinuation of a misused drug if illicit drug use is not known, such as in an unconscious patient or one who voluntarily withholds details of their history. Withdrawal and severity may be diagnosed using the Clinical Opiate Withdrawal Scale (Fig. 27.2) using symptoms such as dysphoric mood, nausea or vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilation or piloerection or sweating, diarrhea, yawning, fever, or insomnia. The time to onset of withdrawal symptoms depends on the type of opioid used. Short acting opioids such as heroin have an onset of withdrawal at 8–24 h after last use and may last 4–10 days. Long-acting opioids such as methadone have an onset of withdrawal symptoms 12-48 h after last use and may last 10–20 days.

Hyperalgesia. Hyperalgesia is an increased sensitivity to painful stimuli. Patients with OUD report a pain sensitivity increase of 42%–72% compared with controls.[37,38] The mechanisms of hyperalgesia can be attributed to central activation of *N*-methyl-D-aspartate (NMDA) receptors and protein kinase C, upregulation of spinal dynorphin, and apoptosis of spinal dorsal horn neurons.[39–41] Patients with OUD maintained on methadone may be hyperalgesic and cross-tolerant to the anti-nociceptive effects of very high plasma morphine concentrations. Higher morphine doses may achieve pain relief, although there is a risk of respiratory compromise.[42]

Tolerance. Tolerance is thought to involve opioid receptor desensitization, internalization, and downregulation, whereas dependence and withdrawal are primarily because of opioid receptor counter adaptation.[43] Clinically, which is defined as an increasing requirement of a drug to gain the same effect. However, different opioids develop tolerance at different rates and different degrees; this is called differential tolerance.[44] For opioids, the development of tolerance is most profound for analgesia, followed by respiratory depression, and finally peripheral effects such as decreased gastrointestinal motility. Thus patients with OUD will be tolerant to the analgesic effects of opioids but may still have an increased risk of respiratory depression if the pain is treated with opioids.[44]

Psychological Comorbidities. There is a high association of substance use disorder with CP despite the absence of clear-cut directional causality.[45,46] Patients with CP often have SUD involving other substances such as benzodiazepines, alcohol, and cannabis.[47–49] CP patients also have a high incidence of psychological comorbidities, including major depressive disorder, anxiety spectrum disorders, post-traumatic stress disorder, and risk of suicide.[50] Data suggests that CP is a significant independent risk factor for suicidality.[51] Predictors of suicidality included frequent intermittent pain, sleep problems, and feeling negative about self-mental health. Interestingly, pain duration, intensity/severity, or type were unrelated to suicide risk.

Patient's Namef_____ Date and Time:___/____/___:_____

Reason for this assessment: _____

Resting Pulse Rate: _____beats/min.
Measured after patient is sitting or lying for 1 min.
0 pulse rate 80 or below
1 pulse rate 81-100
2 pulser rate, 101-120
4 pulse rate greater than 120

GI Upset: *over last 1/2 hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 multiple episodes of diarrhea or vomiting

Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Tremor *observation of outstretched hands*
0 no tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness *Observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Yawning *Observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
3 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable or anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint Aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh Skin
0 skin is smooth
3 piloerection of skin can be felt or hairs standing up on arms
5 prominent piloerection

Runny Nose or Tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

Total Score: _____
The total score is the sum of all 11 items

Initials of person completing assessment: _____

Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

• **Figure 27.2** The Clinical Opiate Withdrawal Scale (COWS). COWS is an 11 item scale designed to monitor the symptoms and severity of opiate withdrawal over time. Score: 5–12, mild; 13–24, moderate; 25–36, moderately severe; >36, severe withdrawal. Revised from Wesson and Ling 2003.[194]

Evaluation of Patients With Opioid Use Disorder who Present for Surgery

Evaluation of both inpatients and outpatients with OUD is best accomplished using a multispecialty approach, including psychiatry, psychology, social work, physical therapy, and/or pain management specialists. Similar to the evaluation of patients with CP and SUD, patients should undergo a comprehensive assessment that includes their substance use history, whether they have active addiction or are in treatment, their comorbidities (including CP history and psychiatric history), a physical examination, and the patient's current mental status.[52] A thorough history and physical examination should include prescription-controlled medication use (which should be verified according to the state's prescription drug monitoring program), the dose of medications taken, use of recreational drugs, pain goals, withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety, and shivering (Table 27.3), and even potentially a urine toxicology screen for controlled and

TABLE 27.3 Symptoms of Opioid Withdrawal, Grouped Into Categories Based on the Organ System Affected

Table 3. Opioid Withdrawal Symptoms	
Gastrointestinal distress	Abdominal cramps Diarrhea Nausea Vomiting
Flu-like symptoms	Lacrimation, rhinorrhea, diaphoresis, shivering, piloerection
Sympathetic arousal	Mydriasis Hypertension Tachycardia Tremor Myalgia/arthralgia
Psychological symptoms	Anxiety Irritability Dysphoria Insomnia Agitation
Other	Yawning, sneezing

illicit medications. If the patient had a history of CP, the baseline pain intensity at rest and during activity should also be assessed. In patients admitted for non-elective surgical procedures, perioperative (particularly post-surgical) withdrawal symptoms should be anticipated. For patients who will require postoperative pain management with opioids postoperatively, especially those who will be discharged with an opioid prescription, screening for opioid abuse risk may occur. While it is assumed that a history of OUD predicts increased risk, the degree of risk can be further anticipated with a simple screening tool. For example, the "ORT" scores patients based on their family history of substance use, personal history of substance use, age, history of preadolescent sexual abuse, and psychological disease.[11]

Patients With OUD in Remission who Present for Surgery

Patients with OUD in remission and without medication treatment may no longer have signs and symptoms of physical dependence, but will continue to be susceptible to triggers. Triggers for relapse include stress (i.e. surgery) and administration of the agents of abuse (i.e. opioids). Thus these patients are at a particularly high risk of relapse. Anxiety surrounding surgery, perioperative concerns (e.g. financial, social, and/or professional), and postoperative pain are stressors that can trigger drug cravings and relapse,[53] as may poor pain control, if it occurs perioperatively.[54,55] An acute pain consultation, even prior to surgery, can help with the development of a safe and effective perioperative pain plan, which may include regional anesthesia, multimodal pharmacologic therapy, and discharge planning.[56] Discharge planning may include storage and disposal of unused opioids and enlisting the help of a responsible friend or family member to assist in managing the patient's opioid use. Overdose prevention education and naloxone prescription should be considered.[57]

Management of postoperative pain in patients with OUD on MAT should start with the continuation of the home medication treatment regimen. Therapy should be based on the degree of expected pain, which depends on the type of surgery and includes, as appropriate, non-opioid adjuvant therapies, regional anesthesia, and nonpharmacologic therapies. Additional opioids can be added, but only when the benefits are deemed greater than the risk. If additional opioids are added, a postoperative tapering plan should be developed to discontinue them after the perioperative phase. Moreover, clear communication should be undertaken with the patient to set expectations and prevent opioid escalation. Multi-disciplinary discharge planning is critical.[58]

Postoperative Pain Management Techniques for Patients With Opioid Use Disorder

Non-opioid Pharmacologic Treatment

Patients on high-dose opioids have a high occupancy rate of opioid receptors, and thus non-opioid methods of pain control allow for the treatment of pain using medications that interact with different pain receptors. The type of medication should be tailored to the type of pain, inflammatory, nociceptive, or neuropathic pain. The use of non-opioid analgesics decreases the need for additional opioids. Most of the available evidence for the efficacy of non-opioid analgesics in reducing and improving perioperative pain is not available in patients with OUD. However, many pain experts recommend maximizing the perioperative use of non-opioid analgesics in patients with OUD when possible. Using a combination of analgesic medications with different mechanisms of action may decrease pain, improve functional outcomes, reduce opioid requirements, and decrease the duration of hospital stay. Although not well studied, even if individual medications only provide mild to moderate improvements in pain outcomes, a combination of agents may have an additive or synergistic effect on postoperative pain.

Intravenous Lidocaine

The pain-alleviating effects of systemic lidocaine in patients with CP conditions have been noted in patients with spinal cord injury,[59] diabetic neuropathy,[60] central pain syndrome,[61] chronic regional pain syndrome,[62] and postherpetic neuralgia.[63] One of the proposed pathophysiologic mechanisms of neuropathic pain is the upregulation of sodium channels in nociceptors. The change in channel density on nociceptor membranes creates an electrochemical environment that causes neurons to reach their depolarization threshold more rapidly, which leads to increased nociceptive signaling. Lidocaine acts as a sodium channel blocker and can modulate neuropathic pain by decreasing the function of these sodium channels, reversing the effects of sodium channel upregulation.[64] While the quality of the evidence is limited and results are variable, lidocaine has been demonstrated to improve postoperative pain scores, decrease opioid consumption, decrease nausea, decrease the duration of hospitalization, and decrease the length of ileus in patients undergoing open or laparoscopic surgery.[65] For instance, Koppert et al. reported a 35% reduction in morphine consumption between 0 to 72 h after surgery in 40 patients undergoing major abdominal surgery.[66] A continuous lidocaine infusion may take 4 to 8 h to achieve a steady state; the context sensitive half-life is 20–40 min after a three day infusion and does not accumulate in healthy individuals.[67] However, pain benefits can persist for many hours or even days after the termination of the infusion, partially because of the anti-inflammatory effects of lidocaine,

which block the activation of polymorphonuclear granulocytes, thus dampening the cascade of inflammatory responses.[65,68] A randomized clinical trial of 180 patients with OUD who underwent orthopedic surgery under general anesthesia were randomly allocated to receive an intravenous infusion of lidocaine, ketamine, or a placebo. Patients who received lidocaine had lower numeric pain scores and opioid consumption 24 h postoperatively than both the ketamine and placebo groups.[69] In addition, patients in the lidocaine group were less restless, calmer, and less drowsy than patients in the ketamine and control group. A 2018 Cochrane review assessed the efficacy of perioperative lidocaine and included 68 randomized controlled trials; the authors concluded that it was uncertain if systemic lidocaine had a clinical impact on pain scores or opioid consumption. The study found a reduction in ileus with a risk ratio 0.37 (95% confidence interval [CI] 0.15 to 0.87), a reduction of time to first bowel movement by a mean of −7.92 h (95% CI −12.71 to −3.13), and a reduction in postoperative nausea with a risk ratio of 0.78 (95% CI 0.67 to 0.91).[70]

N-methyl-D-aspartate (NMDA) Receptor Antagonists

Examples: ketamine, methadone, memantine, amantadine, dextromethorphan.

NMDA receptor antagonists modulate nociception in spinal pain fibers and the central nervous system. Ketamine is the most commonly used NMDA antagonist. At subanesthetic doses, ketamine has been used as an analgesic and to prevent central sensitization,[71] and the spreading of pain sensitivity beyond the original site of injury in the form of secondary hyperalgesia and allodynia. Ketamine can be administered intravenously to both inpatients and outpatients. It can also be used orally and intranasally but is commonly administered intravenously perioperatively. Inpatient delivery and monitoring (e.g. the level of care required, such as telemetry) will depend on institutional protocols. A meta-analysis assessing the efficacy of perioperative ketamine reported a decrease in morphine consumption at 24 h (15.7 mg) and a slight decrease in pain scores at 48 h postoperatively.[72] A meta-analysis assessing the utility of perioperative ketamine included 47 studies in subjects without OUD and found that its use decreased opioid consumption and the time to first analgesic need in the included studies, but with the greatest efficacy in thoracic, abdominal, and orthopedic surgeries. Despite using fewer opioids, 25 out of 32 treatment groups (78%) experienced less pain than the placebo group at some point postoperatively.[73] In patients without OUD taking opioids for CP, a ketamine infusion has been found to decrease average pain scores compared to a placebo, without a change in opioid consumption.[74]

Dextromethorphan is a common antitussive medication and an NMDA antagonist; its affinity with the NMDA receptor is lower than that of ketamine. A meta-analysis of randomized, double-blinded, placebo-controlled trials of subjects without OUD noted that perioperative dextromethorphan use reduced postoperative opioid consumption at 24 to 48 h and pain scores at 1, 4, 6, and 24 h.[75] In a meta-analysis of multimodal preemptive analgesic adjuncts in subjects without OUD benefit was found for preemptive nonsteroidal anti-inflammatory drugs, epidural analgesia, and local anesthetic infiltration, but the effects of ketamine and dextromethorphan were determined to be equivocal.[76]

α-2 Agonists

Examples: Dexmedetomidine, clonidine.

α-2 Agonists act on the a2 receptors of the peripheral and central nervous systems, resulting in sedation, hypnosis, anxiolysis, sympatholysis, and analgesia.[77,78] α2 Agonists appear to potentiate the analgesic effects of opioids.[79]

In a meta-analysis of 28 randomized controlled trials, patients without OUD treated with dexmedetomidine perioperatively reported lower pain intensity at 1 h postoperatively and reduced postoperative opioid consumption at 24 h postoperatively compared to a placebo. In addition, patients demonstrated a lower risk for nausea in the postanesthesia care unit (PACU).[77] In another meta-analysis of 30 trials analyzing both clonidine and dexmedetomidine, both were found to reduce morphine use after surgery. A decrease in morphine use was observed for dexmedetomidine from to 2–24 h postoperatively, with a cumulative decrease in morphine of 30%. The decrease in morphine use was observed for clonidine from 12–24 h postoperatively, with a cumulative morphine decrease of 25%.[78] The degree of morphine sparing was stronger than what has been reported with acetaminophen,[80,81] but weaker than with ketamine,[72] or nonsteroidal anti-inflammatory drugs.[81]

Gabapentinoids

Examples: gabapentin, pregabalin.

Anti-convulsants are typically prescribed for the management of neuropathic pain and have demonstrated efficacy in reducing perioperative pain.[82–86] Surgical tissue injury produces neuroplastic changes leading to spinal sensitization, hyperalgesia, and allodynia.[87,88] Anti-convulsant drugs may be important in the modulation of these postoperative neural changes by suppression of sodium channel and calcium channel activity and suppression of the glutamate action on the NMDA receptor in both the peripheral and central nervous systems.[89]

Gabapentin is an anti-convulsant that blocks the α-2-δ subunits of voltage-dependent calcium ion channels and has been found to reduce postoperative pain and opioid requirements when administered as a single 300–1200 mg dose in patients without OUD.[83,84,90,91] In meta-analyses of spine surgery patients without OUD, gabapentin was found to decrease pain, opioid use, and urinary retention.[91,92] However, in a meta-analysis assessing the effect of gabapentin after total knee arthroplasty, no difference in pain scores was found compared to a placebo.[93]

Pregabalin is similar in mechanism to gabapentin but is more potent with fewer side effects.[94] Pregabalin has been found to have similar benefits to gabapentin perioperatively.[85,95,96] In a systematic review, pregabalin improved postoperative analgesia and reduced morphine equivalent postoperatively than with a placebo.[85,97] Similarly, in a meta-analysis of knee arthroplasty, pain was reduced by approximately 0.5 on an 11 point numeric rating scale.[93] A meta-analysis of patients undergoing hysterectomy concluded that pregabalin decreased pain, morphine consumption, and postoperative nausea and vomiting (PONV).[98,99] When 100–300 mg is used, no difference in acute pain outcomes have been found when a single preoperative dose of pregabalin is given or multiple doses perioperatively.[85] In a meta-analysis of studies in which patients underwent bariatric surgery, a single preoperative dose of 75 mg pregabalin did not improve pain relief, quality of postoperative recovery, or reduction in opioid consumption.[100] However, this may have been because of the low dosage and large volume of distribution in the patient population. This is supported by a dose study in spine surgery patients in which 150 mg pregabalin administered before surgery and 12 h after surgery resulted in decreased opioid consumption. However, the lower dose of 75 mg before and after surgery produced no significant opioid-sparing effect.[101] Regrettably, both gabapentin and pregabalin have an

emerging potential for misuse, particularly in individuals with OUD,[102] and there may be an increase in the risk of respiratory depression when administered in combination with opioids.[103]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Examples: ketorolac, celecoxib, naproxen, ibuprofen.

In meta-analyses of trials with subjects without OUD, postoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to decrease pain across a wide range of surgeries, including lumbar spine surgery,[104] laparoscopic cholecystectomies,[105] and cesarean deliveries,[106] but not dental surgery.[107]

Ketorolac is a non-selective cyclooxygenase (COX)-1 inhibitor that has been found to decrease postoperative pain, and some studies have found a decrease in the need for opioids by 25%–45%.[108–111] Traditionally, 15–30 mg is administered intravenously to adults every 6–8 h. Even 10–15 mg ketorolac is effective in decreasing pain after spine surgery patients and in patients who present to the emergency department with pain.[112,113] Other medications such as celecoxib,[114,115] naproxen,[116,117] and ibuprofen[118,119] have also been shown to decrease postoperative pain. In a study assessing postoperative pain management and comparing ibuprofen 400 mg, oxycodone 5 mg, the combination of ibuprofen-oxycodone 400 mg–5 mg, and a placebo, the number needed to treat (NNT) for a 50% pain reduction was similar for ibuprofen and ibuprofen-oxycodone (NNT 2.3 [2.0–2.8]) than with oxycodone alone (NNT 2.9 [2.3–4]), and the combination of ibuprofen-oxycodone provided analgesia for longer than oxycodone alone.[120] In another study, the NNT for a 50% pain reduction was 2.9, for ketoprofen 50 mg, 2.5, ibuprofen 400 mg, and 2.7 for diclofenac 50 mg.[121]

Acetaminophen

Examples: N-acetyl-para-aminophenol (APAP), acetaminophen.

The mechanism of action of acetaminophen may involve inhibition of peroxidase reactions in the prostaglandin synthesis pathway.[122] A single dose of acetaminophen prior to surgery provides 4 h of effective analgesia for approximately half of patients with acute postoperative pain. The NNT with acetaminophen postoperative is five to prevent one rescue medication administration over 4–6 h.[123] Intravenous acetaminophen has been shown to reduce visual analog pain scores by 1.6 (95% CI, 1.0–2.2) and decrease morphine consumption by 30% in the first 4 h after surgery compared to a placebo.[124] In a separate study, acetaminophen led to a morphine sparing effect of 20% in the first 24 h postoperatively.[80] While acetaminophen has been found to be efficacious by itself, a Cochrane review found that ibuprofen combined with acetaminophen provided better analgesia than either drug alone at the same dose and with a smaller chance of an adverse event.[125] In a randomized controlled trial of intravenous ibuprofen versus acetaminophen in bariatric patients without OUD, both drugs reduced morphine consumption to similar degrees, but ibuprofen was superior in terms of pain relief.[118]

Muscle Relaxants

Examples: baclofen, diazepam, carisoprodol, tizanidine, methocarbamol.

While there is evidence that gamma-aminobutyric acid (GABA)–acting muscle relaxants hinder the release of substance P in animal models,[126,127] evidence for their efficacy in reducing postoperative pain is lacking.

Muscle relaxants should not be stopped perioperatively because of the risk of withdrawal. In 2020, an active clinical trial assessed the effect of a single oral dose of baclofen on postoperative pain and opioid consumption in non–opioid-naïve patients.[128] Intrathecal baclofen as an adjuvant in spinal anesthesia for total knee arthroplasty, decreased postoperative opioid usage, and decreased persistent post-surgical pain at three months after surgery.[129] Diazepam binds to $GABA_A$ receptors and potentiates GABAergic activity by increasing chloride conductance, resulting in presynaptic inhibition in the spinal cord. Diazepam is the only benzodiazepine that has been approved by the Food and Drug Administration for the treatment of spasticity and muscle spasms and is commonly prescribed for these symptoms. However, it is rarely recommended as a first line agent because of the risks of sedation and the potential for dependence or abuse.

No published studies have assessed the efficacy of methocarbamol for postoperative pain, but one study assessing its efficacy after a traumatic injury did not find improved pain control during the first three days of hospitalization.[130] Administration of 4 mg tizanidine prior to laparoscopic cholecystectomy was found in one study to reduce postoperative pain, opioid consumption, and the length of stay in the postoperative recovery unit.[131] In another study, the use of tizanidine after hernia repair decreased pain, increased time to first analgesic, and decreased total analgesic use postoperatively.[132]

Caffeine

Caffeine is a naturally occurring compound that acts on the central nervous system as a stimulant, and its anti-nociceptive actions have been linked to the antagonism of the adenosine receptors and blocking sites of prostaglandin synthesis.[133] A Cochrane review of caffeine as an analgesic adjuvant found caffeine combined with commonly used non-opioid analgesics (e.g. aspirin, NSAIDs, acetaminophen) to improve the duration and efficacy of analgesia without increasing side effects, and about 5%–10% more patients achieved a >50% pain relief with the addition of caffeine, leading to an NNT for caffeine alone to be 15.[134] Another Cochrane review assessing the efficacy of ibuprofen plus caffeine found the combination of 200 mg ibuprofen and 100 mg caffeine to have an NNT of 2.1 to achieve a >50% pain reduction.[135] In a 2019 Phase I trial, caffeine ingestion with aspirin or paracetamol was not found to alter the blood serum concentrations of those agents, suggesting caffeine enhances the analgesic efficacy of these drugs by pharmacodynamic rather than pharmacokinetic interactions.[136]

Esmolol

The analgesic effects of β-blockers have been reported in the treatment of allodynia in humans.[137] β-Blockers are also used to reduce the stress response and decrease the need for opioids following surgery.[138] A meta-analysis found that intraoperative esmolol use reduced intraoperative and PACU opioid consumption, with no change in PACU pain scores.[139] In bariatric surgery patients without OUD, patients who received intraoperative esmolol infusion had similar pain scores compared to those who received epidural analgesia; the two groups also exhibited similar rates of PONV.[140] In elective laparoscopic cholecystectomy, intraoperative esmolol infusion was not inferior to lidocaine infusion in terms of opioid requirement and pain severity in the first 24 h after surgery.[141]

Dexamethasone

Steroids are useful as adjuvant therapy for CP conditions, including metastatic bone pain, neuropathic pain, and visceral pain. Corticosteroids have been shown to reduce inflammation, edema, and spontaneous discharge in an injured nerve, which reduces

neuropathic pain.[142] Dexamethasone is the most commonly used corticosteroid because of its lack of mineralocorticoid effects, long half-life, and higher potency than other corticosteroids. Several meta-analyses assessing the efficacy of dexamethasone for perioperative pain management have concluded that it effectively reduces postoperative pain and opioid consumption.[143–145]

Lidocaine Patches

Transdermal lidocaine has been used to treat both acute and CP. Transdermal lidocaine has been found to be effective for the relief of pain in patients with postherpetic neuralgia and diabetic neuropathy.[146] In a study of patients who received a midline incision for gynecologic surgery, lidocaine patches applied to the incision resulted in reduced postoperative pain scores at rest. However, it did not result in reduced pain scores with activity, morphine consumption, or duration of hospital stay.[147] However, a meta-analysis that assessed its efficacy in the management of acute postoperative pain did not find a significant benefit for pain, opioid consumption, or hospital length of stay.[148]

Cannabinoids

In 2020, many clinical trials assessing the use of cannabinoids for acute and CP were conducted at clinicaltrials.gov. Cannabinoids may help manage some types of CP. A Cochrane review of cannabis-based medicines for neuropathic pain concluded that a higher proportion of patients experienced >50% pain relief compared with a placebo (21% versus 17%).[149] However, at this time, evidence for the efficacy of cannabinoids in managing postoperative pain suggests that they are not helpful.[150]

Regional Anesthesia: Neuraxial Blockade, Peripheral Nerve Blocks, and Local Infiltration

The use of regional anesthesia in patients with OUD who undergo surgery has not been extensively studied. However, there is significant evidence for the efficacy of regional anesthesia in improving postoperative pain compared to parenteral opioids.[151] Therefore most experts recommend the use of continuous regional anesthesia for patients with OUD who present for surgery when possible. Epidural analgesia, regardless of the location of catheter placement, time of pain assessment, or infusing agent, provides better postoperative analgesia than parenteral opioids and IV patient-controlled analgesia (PCA).[152,153] A Cochrane database review of nine randomized controlled trials showed that continuous epidural analgesia provided superior pain control 72 h after abdominal surgery compared with IV PCA alone.[154] A meta-analysis of elderly patients undergoing abdominal surgery found that the addition of epidural opioids to local anesthetics results in improved postoperative pain control.[155]

Peripheral nerve blocks for surgery of the extremities are also beneficial for managing postoperative pain. Specific regional anesthetic techniques have been discussed in detail elsewhere. For all surgeries, continuous peripheral nerve block, regardless of catheter location, provides superior postoperative analgesia, decreased opioid usage, and decreased opioid-related side effects than with opioid analgesia.[156] For abdominal surgery, transversus abdominus plane (TAP) blocks lead to a lower postoperative requirement for morphine at 24 and 48 h than with placebo.[157] If regional anesthesia is not used, infiltration of local anesthetics into the surgical area may provide some pain relief.[158,159] In a meta-analysis of total knee arthroplasty patients, periarticular local anesthetic infiltration was associated with lower pain scores, reduced opioid consumption, and a higher range of motion at 24 h compared to a placebo or no injection.[158] In lumbar spine surgery, a meta-analysis found that postoperative intramuscular local anesthetic infiltration resulted in a prolonged time to first analgesic and a significantly reduced postoperative opioid demand.[159]

Nonpharmacologic Analgesia Treatment

Overall, there is a paucity of studies assessing many different nonpharmacologic techniques for the treatment of postoperative pain. However, acupuncture and some mind-body therapies (MBTs) have been assessed for the treatment of pain. MBTs include hypnosis, meditation, cognitive behavior therapy, and guided imagery; these modalities have been shown to have a moderate effect on pain outcomes.[160] In a meta-analysis of 29 randomized controlled trials of patients without OUD, hypnosis was found to decrease postprocedural pain compared to standard care.[161] A Cochrane review suggested the efficacy of distraction, hypnosis, CBT, and breathing interventions for helping children with needle-related pain or distress. Unfortunately, the quality of evidence was low to very low.[162] Children who received acupuncture may have decreased postoperative pain and analgesic consumption with higher patient and parent satisfaction scores and no adverse outcomes.[163,164] A systematic review concluded that adults treated with acupuncture for the management of postoperative pain had lower opioid consumption, lower pain scores, and lower incidences of nausea, dizziness, sedation, pruritus, and urinary retention.[165]

Opioids

For patients who present for surgery who are prescribed opioids (non-MAT) chronically preoperatively, opioid medications should be continued perioperatively. If a patient cannot take oral medications post-procedurally, the oral morphine equivalent can be converted into a parenterally dosed opioid and administered on a scheduled basis. For patients with a history of OUD, a perioperative pain management plan that includes opioids should be developed by a multi-disciplinary care team. Opioids should be utilized after all other pain management strategies have been exhausted. The lowest effective dose of opioids should be used, and prescribed opioids should be scheduled rather than as needed.

For inpatient management, intravenous PCA is an effective method with high patient satisfaction in the emergency department (ED) and hospital.[166] For PCA to be most efficacious, patients should be counseled on the importance of delivering a self-bolus prior to painful stimulation, such as physical therapy or dressing changes. If the dose is not adequate to facilitate function, future doses can include a higher rescue bolus from the PCA machine or nursing staff prior to painful stimulation. For opioid tolerant patients, the starting dose recommendation is higher than that of opioid-naïve patients, although no firm consensus or guidelines are available. High opioid receptor affinity drugs, such as fentanyl, are preferred if patients are on MAT. The use of a PCA with basal infusion typically depends on provider preference and institution culture.

Once patients can tolerate oral intake postoperatively, the total dose of opioids required to provide adequate pain control should be calculated. Considering this, baseline home opioid medications should be restarted, plus additional opioids to manage acute pain. Given that patients with OUD have physiologic and psychological dependence, conversion to a non-injectable formulation is ideal. Providers must recognize that higher doses of opioids are

often needed in the setting of both hyperalgesia and opioid tolerance, and it is important to find a balance between the use of higher doses and respiratory depression. For all scenarios, a bowel regimen should be administered to aid gastrointestinal motility.

According to the Centers of Disease Control (CDC) recommendations in 2016, providers should consider offering outpatient naloxone when there are increased risk factors of overdose or concurrent benzodiazepine use.[167] For inpatient care, naloxone orders should be in place, so it is immediately available for use by staff. Most states have laws designed to protect healthcare professionals from civil and criminal liabilities for prescribing and dispensing naloxone.[168,169]

SAMPLE ACUTE PAIN REGIMEN FOR OPIOID TOLERANT PATIENTS

- Calculate home regimen OME; continue fentanyl patch or other long-acting meds for baseline control if patient able to tolerate PO intake
- Consider increasing home scheduled opioids by 30%
- Add short acting opioids to cover acute pain (10%–20% of 24 h baseline home dose), dosed PRN Q1-4 h
- If opt for PCA, may use hydromorphone, fentanyl, or morphine
- Avoid basal infusions unless a pain specialist agrees
- Reduce dose of new opioid by 30%–50% when switching from one opioid to another to account for tolerance

Postoperative Pain Management in Patients Taking Medication Assisted Treatment for Opioid Use Disorder

Patients on MAT for OUD, such as buprenorphine, methadone, or naloxone, require special consideration. As naloxone is an opioid receptor antagonist, it cannot be used to assist with acute pain management and should be discontinued perioperatively after consultation with an addiction specialist. Methadone and buprenorphine are dosed daily for addiction treatment, but their analgesic properties last 6–8 h; thus the continuation of outpatient dosing regimens for addiction is not sufficient for acute perioperative pain management. Patients on MAT require a pain management service consultation, and the physician prescribing the patient's MAT should be contacted.

Methadone

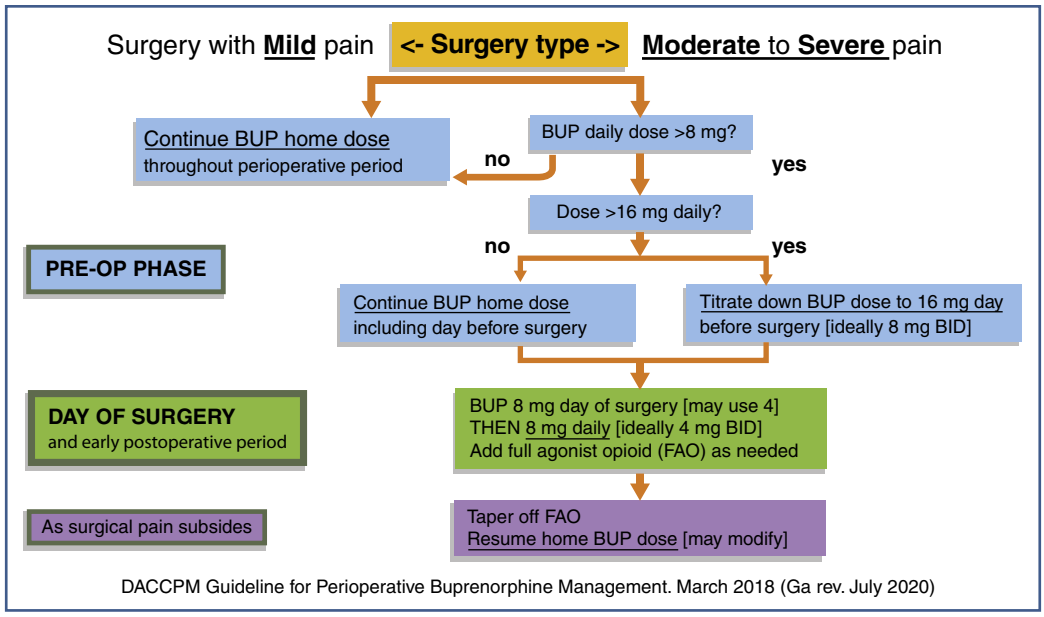
Methadone is a long-acting opioid receptor agonist that reduces opioid cravings by maintaining high levels of opioid tolerance and reducing the euphoric effects of subsequent shorter-acting opioids. As a controlled substance with a potential for abuse, it is only administered by certified SAMHSA opioid treatment programs (OTP). In patients admitted to the hospital, providers should contact the methadone treatment program to verify the dose of the patient and continue that dose in the inpatient setting, including the day of surgery.[170–172] If postoperative oral methadone is not feasible, oral methadone may be switched to the intravenous formulation; the conversion ratio will depend on the patient's baseline dose.[170,173,174] Consultation with a pain specialist is recommended. Non-opioid analgesics, including regional anesthesia, should be employed, and conventional opioid agonists may be used to supplement pain control.[171,172] The provider may also increase the daily methadone dose by 25%–30%, given in divided doses three to four times/day, allowing five to seven days between dose titration.[175] If doses are increased, intermittent electrocardiograms should occur as QT prolongation is a side effect of methadone, especially postoperatively when patients are more susceptible to electrolyte derangement.[176] In addition, monitoring for respiratory depression should occur.[176,177] Prior to discharge, patients should have a follow-up with their OTP for resumption of methadone. The final postoperative methadone daily dose used should also be communicated with the OTP. In opioid-naïve patients, methadone has been repeatedly proven to be a highly effective analgesic for controlling perioperative pain.[178,179] Thus if additional opioids are required for postoperative pain management in patients with OUD, strong consideration should be given to using methadone, both in patients taking methadone for MAT (as above, increased, divided doses) and those who are not.

Buprenorphine

Buprenorphine is a semi-synthetic partial μ opioid receptor (MOR) agonist and an antagonist of the κ-opioid receptor that can be prescribed in a clinician's office for medically supervised opioid maintenance. Although the half-life of buprenorphine is only 3 h, it has a very high affinity for, and a slow dissociation rate from, the opioid receptors to which it binds, leading to a long functional half-life.[180] Buprenorphine is used to treat CP and OUD. In 2007, the World Health Organization (WHO) recognized buprenorphine and buprenorphine-naloxone as a treatment for opioid dependence, including both drugs in the 15th WHO Model List of Essential Medicines. By 2017, at the height of the opioid abuse crisis, 14.6 million buprenorphine prescriptions were dispensed in the United States.[181] With such a high number of prescriptions, many institutions have developed their own protocol for dealing with patients on buprenorphine who present for surgery.[57] Buprenorphine's high affinity for the opioid receptor can be a challenge for treating acute pain, and there continues to be disagreement between practitioners about which has higher priority, acute pain management or continued OUD treatment.

In 2017, a well-cited article in *Anesthesiology* separated those on buprenorphine who were expected to have mild postoperative pain and moderate to severe pain postoperatively. The authors suggested that for patients with moderate-severe pain expected, tapering and cessation of buprenorphine should occur prior to elective surgery, and expectations should be for higher opioid use postoperatively.[182] The authors further suggested that multimodal analgesia should be maximized for all patients, including regional anesthesia, and follow up should be coordinated with the buprenorphine provider. In 2018, guidelines were established by *the pain physician.* Based on a review of 12 articles, providers were advised to discontinue buprenorphine three to five days preoperatively for patients with expected moderate-to-severe postoperative pain and to prescribe full opioid agonists until surgery.[183] However, discontinuation of buprenorphine in the highly stressful, emotionally charged perioperative period risks precipitation of OUD relapse.[184]

If postoperative pain is expected to be mild, most providers suggest continuing the baseline dose of buprenorphine and supplementing with multimodal analgesics.[182] If postoperative pain is expected to be mild-moderate, some clinicians suggest increasing the daily dose of buprenorphine (maximum 32 mg/day) and giving it in divided doses every 6–8 h.[183,185] Literature from 2019 and 2020 suggests that if moderate-to-severe postoperative pain is expected, buprenorphine should be continued, but decreased to 12–16 mg/day preoperatively (for those taking >16 mg/day).[182,186–188] Continuing buprenorphine



• **Figure 27.3** The protocol implemented at Massachusetts General Hospital (MGH) in March 2018. *BID,* "Bis en die" (twice/day); *BUP,* buprenorphine; *DACCPM,* department of anesthesia, critical care, and pain management at MGH; *mg, milligram; PRE-OP,* preoperative. Adapted with permission from Acampora et al. 2020.[186]

perioperatively, even at a lower than normal dose, should continue to provide OUD relapse risk mitigation. On the day of surgery and in the acute postoperative phase, if moderate-to-severe postoperative pain is expected and the daily dose is >16 mg, buprenorphine can be divided into two doses[186] (Fig. 27.3). A daily dose of buprenorphine 16 mg binds to approximately 70%–90% of μ-opioid receptors.[189]

For patients 1) who were administered monthly buprenorphine injections, 2) were scheduled for elective surgery, 3) whose daily dose of buprenorphine is >16 mg, and 4) are expected to have moderate-to-severe postoperative pain, it may be prudent to switch the patient to daily buprenorphine. For patients using the buprenorphine month implant, as the daily dose is about 8 mg/day once steady state is achieved after four weeks,[190] it should probably be continued. When pain subsided postoperatively, if additional opioid agonists were prescribed, they should be tapered and discontinued with a return to the patient's preoperative buprenorphine dose. A detailed plan should be developed preoperatively with the patient's prescription of buprenorphine.

Naltrexone

Naltrexone is an opioid antagonist that competitively binds to opioid μ receptors and can be taken as an oral formulation or a monthly intramuscular injection. Perioperative planning is ideal for discussing the risks and benefits of different options with the patient. Postoperative pain management is a clinical challenge for patients receiving naltrexone for the treatment of OUD and should include preoperative communication with the patient's naltrexone prescription.[191] For those who are on an oral formulation, naltrexone should be discontinued 72 h before surgery. For those prescribed subcutaneous injections, surgery should be scheduled for at least four weeks after the last injection. If emergency surgery is performed while the patient is on naltrexone, higher doses of opioids are required to overcome its MOR antagonist activity.[192] In contrast, when naltrexone does not occupy the receptors, opioid analgesics can elicit an exaggerated response because of opioid receptor upregulation, resulting in more exaggerated responses to opioid medications.[193]

Conclusions

Postoperative pain management in patients with OUD is complex and benefits from a cooperative multi-disciplinary treatment plan. The perioperative period is a vulnerable time for patients with OUD, as they may face adverse judgment and undertreatment of their pain because of the presence of opioid tolerance, hyperalgesia, withdrawal, and likely comorbid psychiatric disorders. A multimodal approach to pain management in patients who present for surgery with a history of OUD is highly recommended. This multimodal approach should include, as appropriate, non-pharmacologic therapies, regional anesthesia, and non-opioid analgesics. Opioid analgesics should be used only when necessary and after a risk-benefit analysis. For patients who undergo surgery with MAT for OUD, methadone should be continued perioperatively. However, to provide adequate analgesia, methadone should be administered in divided doses, not once a day. There is compelling evidence that methadone improves postoperative pain compared to other opioids in opioid-naïve patients who undergo surgery. Thus for patients with OUD, consideration should be given to increasing the patient's baseline dose of methadone postoperatively, when appropriate, to improve postoperative pain management. Many pain specialists now suggest that for patients with OUD managed with buprenorphine and who present for surgery, buprenorphine should be continued perioperatively to decrease the risk of OUD relapse and allow for adequate pain management. Patients with OUD who present for surgery must be closely monitored, and a perioperative strategy, including an opioid taper plan for those who require additional opioids, should be developed preoperatively.

Key Points

- Over 2.1 million Americans (0.7%) and 16 million people worldwide have OUD.
- Patients with OUD have a significantly increased mortality risk than those without OUD.
- Acute pain management for patients with OUD must occur within a risk minimization framework.
- Treatment for OUD should continue to occur during the perioperative period, especially MAT, as it has been shown to be the most efficacious in preventing relapse.
- Management of postoperative pain in patients with OUD necessitates an interdisciplinary care team.
- Perioperative challenges when managing pain in patients with OUD include hyperalgesia, opioid tolerance, the potential for withdrawal, and a high incidence of additional psychiatric comorbidities.
- Evaluation of patients presenting for surgery with OUD should include questions regarding whether the patient is in remission or not, past and current illicit substance use, and the amount and type of current substance use, including medication-assisted therapy.
- Postoperative pain management should maximize regional anesthesia, non-opioid pharmacologic, and nonpharmacologic therapies before opioid analgesics are employed.

Suggested Readings

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28

Evaluation and Treatment of Acute Pain in Children

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Recognition and treatment of acute pain is a vital component of pediatric medicine.[1,2] Adequate pain control is necessary to prevent adverse neurohormonal and developmental changes in response to painful stimuli.[3–5] Fortunately, advances in pharmacologic therapy and regional anesthesia techniques have helped expand the scope of pediatric acute pain management.[6] In addition, the establishment of pediatric acute pain services has played an important role in ensuring timely and consistent care of children.[7,8]

Developmental Neurobiology of Pain

The study of pain in neonates has been a significant focus in the field of neuroscience. Nociceptive pathways are well developed even at birth, resulting in hormonal, metabolic, cardiorespiratory, emotional, and behavioral changes in response to painful stimuli.[9] A study of brain perfusion in response to pain has demonstrated significant changes in perfusion with noxious stimuli versus non-noxious stimuli.[10] Newborn rats appear to have a significant proliferation of A and C fibers with a pattern of hyperalgesia developing at sites exposed to painful stimuli.[11] Analogously, human neonates exposed to repeated heel sticks develop cutaneous hyperalgesia, which can be reversed with topical local analgesia.[12] Therefore it is a misconception that pain control is less important in neonates and small children because they cannot form memories of painful experiences or communicate discomfort. Adequate analgesia can limit the immediate and long term effects of noxious stimuli, and treatment of pain in young patients should receive the same level of attention as in adults.

Assessment of Pediatric Acute Pain

Reliable assessment of pain level is essential for effective management.[13] Unfortunately, pediatric patients may be too young, developmentally immature, or unwilling to adequately communicate their pain level.[14] Assessment of acute pain in such patients often relies on observer reports, whereas older children may use self-report measures (see Table 28.1).[15–30] Observational pain assessment tools rely on the interpretation of pain related activity such as body movements, facial expression, and vocalizations; physiologic changes such as heart rate and oxygen saturation; and the child's behavioral state. These measures have been designed to assess procedural pain (e.g. premature infant pain profile [PIPP],[16] neonatal facial coding system [NFCS][17]) or postoperative pain (e.g. Children's Hospital of Eastern Ontario pain scale [CHEOPS],[31] toddler-preschooler postoperative pain scale [TPPPS]).[23] The FLACC scale (faces, legs, activity, cry, consolability) is a tool that can be used for all ages,[32,33] while the revised FLACC (rFLACC) scale incorporates additional observable behaviors to improve validity in children with cognitive impairment (see Table 28.2).[34] The rFLACCs ease of use and validation in patients with a wide range of ages and cognitive levels make it a practical choice for assessment of patients who cannot self-report. Observational assessment tools have limits in their specificity, particularly when including physiologic parameters that can vary because of conditions not associated with pain. Despite their intrinsic limits, these scales have been shown to have construct validity and internal and interrater reliability.[18–22,24–30]

Developmentally appropriate children five years and older can typically provide self-reports on one of several validated visual analog (e.g. colored analog scale [CAS][26]) or faces scales (e.g. faces pain scale-revised [FPS-R],[19,35] Oucher[21]) (Fig. 28.1). McGrath and Hillier[36] developed a separate facial affective scale designed to measure pain affect, as distinct from pain intensity. Interestingly, the faces scales anchored with a smiling face produce higher pain ratings than do those anchored with a neutral face.[37] Discordance between an observer's ratings of a child's pain and the child's self-report is well described.[38,39] Therefore the child's self-reported pain level should be considered the "gold standard" whenever it can reliably be obtained.[40]

The majority of pediatric pain assessment measures that have been developed focus on acute, procedure-related pain.[41,42] Alterations in the behavioral and sensory aspects of pain that can habituate when pain becomes chronic may not be captured by these measurement scales.[38] A systematic evaluation of chronic pain in children is beyond the scope of this chapter (see Chapter 42).

Nonmedical Management of Pediatric Acute Pain

Management of pain through nonmedical techniques (e.g. environmental and behavioral strategies) has proved effective in modulating pain, both independently and in conjunction with pharmacologic interventions in children.[43–47] Cognitive behavior therapy (e.g. relaxation, problem solving, cognitive coping skills) and distraction techniques such as deep breathing, cartoon videos, party blowers, and hypnosis have strong empirical support for their efficacy in easing procedure-related pain in children.[48–51]

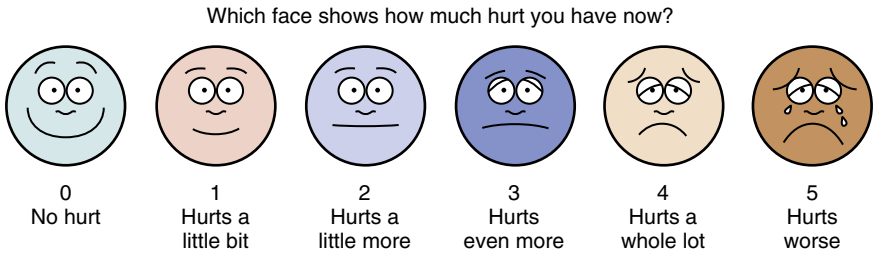
TABLE 28.1 Clinical Measurements of Pediatric Acute Pain

Age Group	Measure	Type of Measurement	Type of Pain
Neonates and infants	Premature infant pain profile (PIPP) (preterm and full-term neonates)[16]	Behavioral, physiologic, gestational age	Procedural
	Neonatal facial coding system (NFCS) (preterm and full-term neonates, infants ≤18 months)[17]	Behavioral	Procedural
	COMFORT scale (zero to three years)[18]	Behavioral, physiologic	Procedural, postoperative
	rFLACC scale (two months to seven years)[32–34]	Behavioral	Postoperative
Toddlers and preschoolers	Faces scales[19,20]	Self-report	Procedural, postoperative
	Oucher (≥ three years)[21]	Self-report	Procedural
	Poker chip tool (four to eight years)[22]	Self-report	Procedural
	Toddler-preschooler postoperative pain scale (TPPPS) (one to five years)[23]	Behavioral	Postoperative
	Children's Hospital of Eastern Ontario pain scale (CHEOPS) (one to seven years)[24]	Behavioral	Postoperative
	Children's and infants' postoperative pain scale (CHIPPS) (zero to four years)[25]	Behavioral, physiologic, alertness, calmness	Postoperative
	rFLACC scale (two months to seven years)[32–34]	Behavioral	Postoperative
School-age children and adolescents	Colored analog scale (CAS) (≥ five years)[26]	Self-report	Procedural, recurrent, chronic
	Visual analog scale (VAS) (≥ five years)[26,27]	Self-report	Procedural, recurrent, chronic
	Faces pain scale	Self-report	Procedural, recurrent, chronic
Non-communicating children, children with cognitive impairment	Non-communicating children's pain checklist-postoperative version (NCCPC-PV), non-communicating children's pain checklist-R (NCCPC-R)[28,29]	Behavioral	Procedural, postoperative injury, pain related to a chronic medical condition
	VAS[30]	Self-report	Procedural
	rFLACC scale [32,34]	Behavioral	Postoperative

TABLE 28.2 Revised FLACC Behavioral Pain Scale

Categories	Scoring 0	Scoring 1	Scoring 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested, *appears sad or worried*	Frequent to constant frown, clenched jaw, quivering chin, *distressed-looking face; expression of fright or panic*
Legs	Normal position or relaxed, *usual tone and motion to limbs*	Uneasy, restless, tense, *occasional tremors*	Kicking or legs drawn up, *marked increase in spasticity, constant tremors or jerking*
Activity	Lying quietly, normal position, moves easily; regular rhythmic respirations	Squirming, shifting back and forth, tense, *tense, or guarded movements; mildly agitated (e.g. head back and forth, aggression); shallow, splinting respirations, intermittent sighs*	Arched, rigid, or jerking, *severe agitation; head banging; shivering (not rigors); breath holding, gasping or sharp intake of breaths, severe splinting*
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint, *occasional verbal outburst or grunt*	Crying steadily, screams or sobs, frequent complaints, *repeated outbursts, constant grunting*
Consolability	Content, relaxed	Reassured by occasional touching, hugging, being talked to; distractible	Difficult to console or comfort, *pushing away caregiver, resisting care or comfort measures*

Non-italicized text denotes the original FLACC descriptors. Italicized text denotes behaviors that were added for the revised FLACC scale, improving validity for assessment of children with cognitive impairment.[34]



• **Figure 28.1** Faces pain scale.

Distraction methods are hypothesized to work by engaging children and redirecting their attention away from the pain, thereby reducing perceived pain intensity and inhibiting the neural activity that underlies pain perception.[52–58] Complementary and alternative medicine techniques such as acupuncture have also been described as potential treatments of acute pain in children.[59,60]

Recent studies have identified preoperative risk factors for worse postoperative pain, including patient behaviors such as catastrophizing and psychological and somatic symptoms such as depression and fatigue.[61–63] Additional research is needed to determine whether psychological and other nonpharmacologic interventions may be beneficial for this pain-vulnerable group of children.

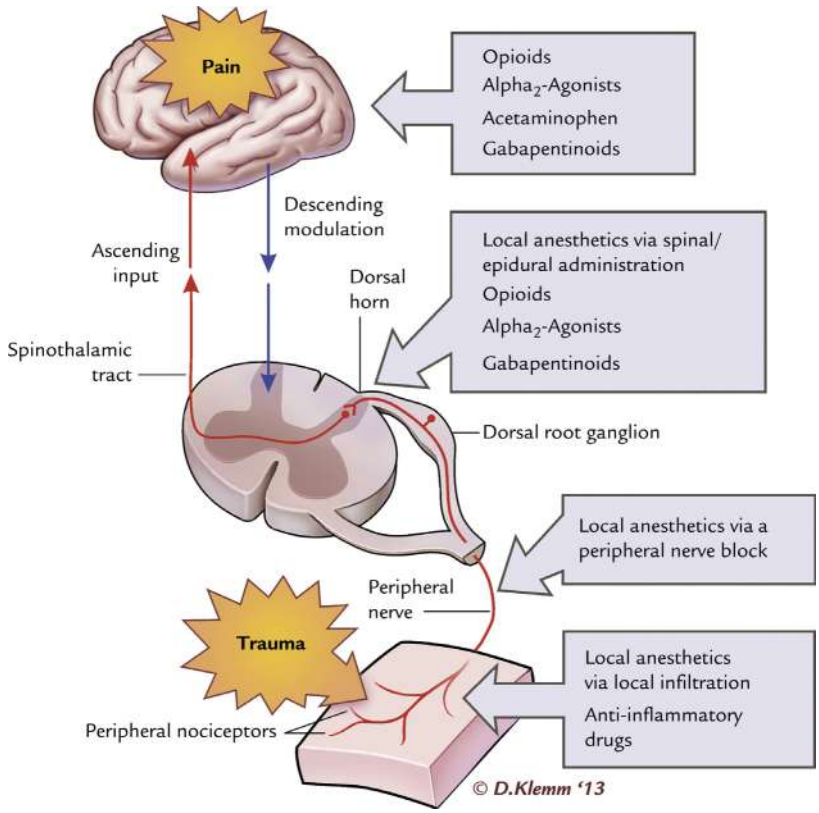
Pain Treatment Modalities

Acute pain in infants and children may result from several causes, including surgery, trauma, sickle cell vaso-occlusive episodes, and oncologic processes and treatments. Non-opioid analgesics can provide adequate control of mild pain with minimal side effects.[64] For moderate to severe pain, a multimodal strategy that incorporates non-opioid analgesics, opioids, and regional anesthesia is preferred. Multimodal analgesia involves multiple agents working synergistically at different biologic locations along the pain pathway (Fig. 28.2).[65] This allows improved pain control with reduced side effects (sedation, respiratory depression, nausea, pruritis, ileus) that can occur with the higher doses required when opioids are used alone for treatment of severe pain.[66,67] Patient factors such as comorbidities, developmental level, opioid use history, and ability to take oral medications must be considered along with pain cause, severity, location, and expected duration when developing an optimal analgesia plan.

Non-opioid Analgesics

Sucrose

Oral administration of glucose and sucrose can provide mild analgesia, as opioid peptides in the ventral striatum and cingulate gyrus may play a role in regulating positive responses to energy-rich food sources.[68,69] A Cochrane database review suggested that sucrose



• **Figure 28.2** The pain pathway and locations of action for various analgesics. (© David Klemm).

may be effective in reducing procedural pain in neonates.[70] Doses in the range of 0.01–0.1 g can be used to reduce procedural pain in infants younger than six months.[71]

Acetaminophen

Acetaminophen is commonly used in children to reduce or eliminate pain from a variety of conditions.[72] It can be administered via the oral, rectal, and intravenous routes. There is no evidence to suggest the superior analgesic effect of one route over another when appropriately dosed, and the oral route is the most cost effective.[73] The rectal and intravenous routes are used for patients unable to take oral medications, as is often the case in the perioperative period. Higher rectal doses (i.e. 30–40 mg/kg loading dose followed by 15–20 mg/kg maintenance doses at 4–6 h intervals in children over two years old) are required to produce therapeutic serum concentrations in the majority of patients, and there is large interindividual pharmacokinetic variability.[74,75] Intravenous acetaminophen has more predictable bioavailability and achieves maximum concentration more rapidly than rectal dosing, and therefore may be the preferred non-oral route for administration to hospital inpatients.[76]

While rare, hepatotoxicity is a dose-dependent risk with acetaminophen use.[77] Compared to older children, neonates exhibit decreased acetaminophen clearance because of renal and hepatic immaturity. Doses should be reduced, especially in preterm infants.[78] Another potential source of overdose is inadvertent administration from multiple sources, including over-the-counter cold remedies and fixed-dose opioid combinations, both of which often contain acetaminophen. All medications being taken by a patient, including those available without a prescription, should be carefully reviewed before recommending acetaminophen (Table 28.3).

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in children and can be administered via oral, intravenous, or intramuscular routes. NSAIDs are an effective treatment for various pain states and have been shown to be more effective than opioids for mild traumatic musculoskeletal pain in children.[79] When used in the postoperative setting, NSAIDs can produce analgesia equivalent to a dose of opioid, and their use with or without additional opioids has been associated with less nausea, vomiting, respiratory depression, and other adverse events.[72,80,81] Ketorolac is commonly used in children and can be administered via intravenous or intramuscular routes.

The clinical significance of the effects of NSAIDs on platelet function remains controversial, which has led to its avoidance by some for procedures with a significant risk of postoperative bleeding. Known side effects, including bleeding, renal toxicity, and gastritis, are more likely to occur with prolonged administration and in the presence of coexisting disease. Adverse events are more common in neonates; NSAIDs should be used cautiously in patients less than six months of age and avoided in patients less than 21 days old or 37 weeks post gestational age.[82,83] Evidence from animal models has caused concern that NSAIDs may interfere with osteogenesis. However, studies of children receiving a short course of NSAIDs, including ketorolac, after spinal fusion or operative fracture repair do not appear to be at increased risk for bone nonunion.[84,85] Aspirin, a unique NSAID that irreversibly inhibits cyclooxygenase (COX)-1 and COX-2, should not be routinely used as an analgesic in patients under the age of 18 years because of the risk of Reye's syndrome, a serious acute encephalopathy.[86]

TABLE 28.3 Non-opioid Analgesic Dosing

Medication	Dose	Dosing Interval (h)	Maximum Daily Dose (mg/kg)	Maximum Daily Dose (mg)
Acetaminophen* (oral)	10–15 mg/kg	4–6	75	3000
Acetaminophen* (IV)	15 mg/kg	6	75	3000
Acetaminophen* (rectal)	30–40 mg/kg as loading dose, 15–20 mg/kg maintenance	6	75	3000
Ibuprofen^	5–10 mg/kg	6–8	40	2400
Ketorolac (IV)^,#	0.5 mg/kg	6	2	120
Celecoxib (oral)	10–25 kg: 50 mg >25 kg: 100 mg	12		400
Gabapentin (oral)	<50 kg: 15 mg/kg loading dose, 5 mg/kg maintenance >50 kg: 300–600 mg	8		
Pregabalin (oral)	<50 kg: no available evidence >50 kg: 50 mg	8–12		
Ketamine (infusion)	0.1–0.2 mg/kg/h	Continuous		
Diazepam (oral, IV)	0.05–0.1 mg/kg	6–8		

*Dose should be decreased in preterm and term neonates.

^Use with caution in neonates <6 months old.

#Avoid use in neonates <37 weeks post gestational age or 21 days postnatal age.

IV, Intravenous.

Gabapentinoids

The antiepileptic medications gabapentin and pregabalin have been used as adjunctive medications for the management of post-surgical pain with a neuropathic component, such as following posterior spinal fusion. While robust evidence for efficacy is currently lacking, one study did suggest improved pain control and decreased opioid use when gabapentin was used following posterior spinal fusion in pediatric patients.[87] No studies have examined the use of these drugs following other surgeries in children, but evidence in adults supports the use of gabapentin and pregabalin following large abdominal surgeries as well.[88]

Ketamine

Ketamine has been investigated as an adjunctive analgesic for pediatric inpatients with several painful conditions. When given as an intraoperative bolus, it has improved early postoperative pain scores, reduced opioid use, and decreased the incidence of emergence delirium.[72] Patients with episodes of acute or chronic pain from sickle cell disease or cancer may particularly benefit from a low-dose ketamine infusion.[89,90] These patients are at risk for poor pain control because of opioid tolerance and opioid-induced hyperalgesia, processes that may be reversed by ketamine's antagonism of the *N*-methyl-D-aspartate glutamate receptor.[91]

Muscle Relaxants

Diazepam is a benzodiazepine with muscle relaxant properties. It is commonly used to relieve pain from muscle spasms following orthopedic surgeries involving dissection through large muscle groups, such as posterior spinal fusion for scoliosis and periacetabular osteotomy for hip dysplasia.[92,93] Benzodiazepines cause sedation and respiratory depression, particularly when used concurrently with opioids. Thus respiratory monitoring should be employed when using them together at high doses.[94,95] Other muscle relaxants used in pediatrics include baclofen and tizanidine.

Tramadol and Codeine

Tramadol and codeine, both administered as prodrugs with little intrinsic activity, are metabolized to their active forms by the enzyme CYP2D6.[96] The active form of tramadol is a unique medication with opioid and non-opioid effects. In contrast, codeine is metabolized to morphine, with pure opioid effects. Both were previously used for the control of pain in children.[97,98]

Genetic variants of the CYP2D6 enzyme lead to wide variations in the serum concentrations of the active forms of these drugs. Slow metabolizers produce lower levels of active drug and experience poor pain control, while ultrarapid metabolizers quickly develop very high serum levels of the active drug and are at risk for adverse effects, including respiratory depression.[99] In response to several deaths in children with ultrarapid metabolism of codeine, the Food and Drug Administration (FDA) issued a 2017 warning advising against the use of both of these drugs in nursing mothers, all children younger than 12 years of age, and patients aged 12–18 years at risk for opioid-induced respiratory depression, including those with obstructive sleep apnea, obesity, lung disease, or following tonsillectomy.[100] Therefore codeine has been almost completely replaced by other oral opioid medications for use in pediatric patients. Because of its unique mechanism of action, tramadol still has a role for some pediatric patients with chronic pain. However, tramadol is often titrated to a target dose over days to weeks to prevent side effects such as somnolence and has limited use in the management of acute pain in children.

Opioid Analgesics

Stewardship During the Opioid Epidemic

A crisis of opioid misuse has afflicted the United States over the first two decades of the 21st century, with soaring rates of abuse and overdose deaths. While the opioid epidemic has received widespread attention, most legislative action and treatment programs have been aimed at adults. Unfortunately, children of all ages have also been affected, and anyone treating pediatric pain must be aware of the ways their patients may be affected by this national crisis.[101]

Opioid use during pregnancy has resulted in rising rates of neonatal abstinence syndrome (NAS), with about 32,000 infants now diagnosed per year in the United States. NAS may result in dysregulation of the central nervous, autonomic nervous, respiratory, and gastrointestinal systems, requiring a high level of neonatal care to prevent further morbidity. NAS also complicates pain management for affected infants undergoing painful procedures and may have additional long-term physical, psychological, and behavioral effects which have yet to be fully characterized.[102]

Toddlers and young children living in homes with opioid-using adults are at significant risk for accidental ingestion and overdose.[103] The increasing reservoir of unused opioids in the community has led to a nearly three-fold increase in pediatric opioid overdose deaths from 1999–2016.[104]

Substance use disorders often start in late childhood and adolescence, and the last 20 years have also seen a dramatic increase in opioid abuse and deaths in this population.[105] Even teenagers who are appropriately prescribed opioids for pain relief following surgical procedures are at risk for subsequent misuse and addiction to opioids and other substances.[106,107]

Despite these concerns, opioids are often needed to prevent unnecessary suffering in infants and children. They remain a fundamental component of appropriate pain control strategies for young patients in the postoperative setting and the management of chronic painful conditions such as sickle cell disease, cystic fibrosis, and cancer. To responsibly care for pediatric outpatients with pain, physicians and medical providers should take steps to reduce the chances of accidental or intentional misuse of opioids. Parents should be instructed to keep any opioids in the home safely, preferably locked, where children cannot reach them. Parents should also be told to safely dispose of opioids as soon as the prescribed patient no longer needs them, either at a local drug take-back site, by flushing them down the toilet, or by combining them with dish soap or kitty litter and throwing them in the garbage. Finally, physicians should attempt to reduce the reservoir of unused opioids in the community by prescribing the lowest number of doses that are expected to reasonably care for a patient's pain in the outpatient setting, especially for acute indications such as post-surgical pain.

Opioid Therapy

Opioids may be administered via oral, parenteral, intranasal,[108,109] and neuraxial routes. Opioid clearance is lower in neonates but reaches mature levels in the first six months of life.[110] Opioid-induced respiratory depression may be more pronounced in neonates and infants, as reflexive respiratory responses to airway

TABLE 28.4 Oral Opioid Analgesic Dosing Guidelines

Medication	Potency Relative to Morphine	Typical Starting Dose (mg/kg)	Typical Dose if >60 kg (mg)	Dosing Interval (h)
Morphine	1	0.3	15–20	3–4
Hydrocodone	1–1.5	0.1–0.2	5–10	4–6
Oxycodone	1–1.5	0.1–0.2	5–10	4–6
Hydromorphone	5–7	0.04–0.08	2–4	3–4
Methadone	1	0.1–0.2	10	6–12

TABLE 28.5 Management of Opioid-related Side Effects

Adverse Effect	Initial Management	Secondary Management
Pruritus	Diphenhydramine, hydroxyzine	IV low-dose naloxone[166]
Nausea, vomiting	Ondansetron,	Promethazine, IV low-dose naloxone[166]
Urinary retention	Decrease opioid dose	Urinary catheterization
Respiratory depression	Decrease opioid dose	IV naloxone

IV, Intravenous.

obstruction and hypoxemia mature over the first year of life.[111] Children with obstructive or central sleep apnea are also at high risk for opioid-induced respiratory depression and sedation, and opioids should be started at roughly 50% of the dose for a typical patient of similar age and weight.[112] Starting oral doses for opioid-naïve patients without significant medical comorbidities are listed in Table 28.4. Intravenous opioids are chosen when patients cannot take oral medications or require rapid titration for severe uncontrolled pain.

High doses of opioids are associated with multiple adverse effects, including sedation, respiratory depression, nausea, vomiting, ileus, constipation, pruritus, and itching. These side effects can significantly prolong patient recovery and may be more unpleasant than the pain for which the opioids are being prescribed. Non-opioid analgesics and regional anesthesia should be used to the maximum extent possible in patients with poorly controlled pain, with the goals of reduced opioid requirement, better pain control, decreased side effects, improved functional level, and faster recovery. Management options for opioid-related side effects are shown in Table 28.5.[113]

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) can provide controlled, titratable, autonomous analgesia to children and adolescents. Several trials support the safety and efficacy of PCA in children older than six years.[114] PCA is now the standard method for delivering opioid analgesia for children with severe pain after surgery or in cases where the patient cannot tolerate medication by mouth, such as with chemotherapy-induced mucositis.[115] Patients with severe acute nonsurgical pain, such as sickle cell vaso-occlusive pain or acute worsening of cancer pain, may also benefit from the rapid titration that PCA allows.

Morphine, fentanyl, and hydromorphone are commonly used opioids for PCA. Because PCA-delivered demand boluses are relatively small and chosen to maintain analgesia, pain should be well controlled with a loading dose prior to the initiation of PCA. A continuous infusion of opioids may be paired with PCA to replace chronic opioid requirements or improve sleep patterns for the first night following particularly painful surgery.[116] Continuous infusions often lead to a higher amount of delivered opioids and may make nausea and sedation more likely. Therefore caution should be employed whenever a continuous infusion is used, particularly in patients at risk for respiratory depression.[117–119] Suggested PCA parameters for opioid-naïve patients without significant medical comorbidities are listed in Table 28.6. Continuous pulse oximetry and respiratory monitoring should be routinely employed with PCA, as large amounts of opioids may be delivered.[120]

For young children or those with cognitive impairment, the demand doses of opioids may be administered by a nurse (nurse controlled analgesia, or NCA) or a family member (PCA by proxy, or PCA-P). NCA and PCA-P eliminate a built-in safety mechanism of PCA, which is that the patient must be alert enough to self-deliver additional opioids. Parents must be educated to only deliver demand boluses if the patient is awake and in pain, as providing boluses to a sleeping patient may cause respiratory depression and opioid overdose.[121,122] Despite these risks, NCA and PCA-P can provide safe and effective pain relief when appropriate precautions are taken.[123]

TABLE 28.6 Patient-Controlled Analgesia Dosing Guidelines

Medication	Loading Dose	Demand Dose	Lockout Time (min)	Continuous Infusion
Hydromorphone	10–20 (μg/kg)	2–3 (μg/kg)	5–15	2–3 (μg/kg/h)
Morphine	0.05–0.1 (mg/kg)	0.01–0.02 (mg/kg)	5–15	0.01–0.02 (mg/kg/h)
Fentanyl	0.5–1 (μg/kg)	0.15–0.2 (μg/kg)	5–15	0.15–0.2 (μg/kg/h)

Regional Anesthesia

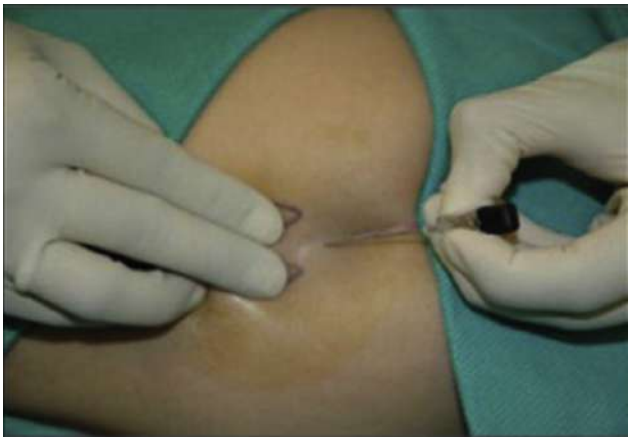
Regional anesthesia is an effective means by which to reduce postoperative pain and opioid use in pediatric surgical patients.[124] Versatile new techniques[125,126] and the adoption of enhanced recovery protocols that include regional anesthesia[127] have contributed to increased utilization. However, the most important factor behind increased use has been the widespread acceptance of regional anesthesia performed on pediatric patients under general anesthesia.

In adults, regional anesthesia is most often performed on awake or minimally sedated patients. Pain or paresthesia may suggest improper needle placement and potential nerve damage, while symptoms such as tinnitus may be early signs of local anesthetic systemic toxicity (LAST) from an inadvertent intravascular injection. General anesthesia may be avoided if surgical levels of regional anesthesia are achieved, which is especially beneficial for adults with high risk comorbidities. Conversely, children are more likely to be afraid of needles and invasive procedures and may not cooperate if fully awake or minimally sedated. Even if symptoms suggesting impending injury were elicited, young or developmentally immature patients may not be able to communicate these to the regionalist. An uncooperative patient may move while the needle is close to delicate structures, increasing the risk for damage.

Needle placement is more accurate with ultrasound visualization, allowing avoidance of nerves and vascular structures and reduction in the volume of local anesthetic needed to achieve the desired result.[128] Large multicenter studies of regional anesthesia in children have shown low complication rates (comparable to those seen in adult practice) and a reduced incidence of LAST and neurologic complications when performed under general anesthesia compared to minimally sedated or awake patients.[129–131] Therefore the performance of pediatric regional anesthesia under general anesthesia or deep sedation is now considered standard of care.[132,133]

Caudal Analgesia

One of the most commonly used pediatric regional anesthesia techniques is the caudal block, which can provide analgesia from the lumbosacral to midthoracic dermatome levels.[134] The caudal block is popular because of readily palpable landmarks, ease and speed of placement in infants and children, and low rates of failure or complications.[135] A needle with a blunt stylet is passed through the sacrococcygeal ligament into the caudal space (Fig. 28.3). A distinct "pop" is felt when the caudal space is entered. Ultrasonography has been described as a tool to assist in caudal placement.[136] Local anesthetics include bupivacaine (0.125%–0.25%) and ropivacaine (0.1%–0.375%), with volumes of 0.5–1.25 mL/kg (maximum volume 30 mL) depending on desired dermatomal level. The most commonly used dosing is 1 mL/kg of ropivacaine 0.2% or bupivacaine 0.25%.[137,138] Because of the difficulty in interpreting a negative test dose, the use of epinephrine 1:200,000 in the caudal solution is discretionary. If epinephrine is used, a heart rate increase of greater than 10 beats per min or any change in T wave morphology in the first minute after injection should be considered an accidental intravenous injection, and needle placement should be adjusted before further injection.[132]



• **Figure 28.3** Caudal block landmarks and placement technique.

Spinal Anesthesia

Former preterm infants are particularly susceptible to the risks of general anesthesia, and spinal anesthesia has been proposed as an alternative for procedures such as inguinal hernia repair.[139] However, this has not become routine practice because of a lack of provider familiarity with the technique and concerns over the duration of spinal anesthesia in cases of unexpectedly prolonged surgery.[140,141] Rates of apnea in the immediate postoperative period may be reduced with spinal anesthesia, but there is no overall impact on apnea incidence in the first 12 h. Therefore this technique does not reduce the need for extended observation of premature infants.[142] While concerns exist over potential neurotoxicity related to general anesthesia in young children, avoidance of a brief general anesthetic through the use of spinal anesthesia for hernia repair has not been found to have any impact on neurodevelopment, further limiting the applicability of this technique.[143,144]

Continuous Neuraxial Catheters

Continuous epidural analgesia is a commonly used technique in infants and children.[145,146] Epidural catheters may be placed in the thoracic, lumbar, or caudal regions. It is also possible to insert a catheter into the caudal space and thread it cephalad to the desired vertebral level, with location confirmation by ultrasound or epidurogram.[147] Bupivacaine and ropivacaine are frequently used local anesthetic solutions. Common additives to these solutions include opioids (e.g. fentanyl, morphine, or hydromorphone) and α2-agonists (e.g. clonidine). Standardized dosing parameters must be used in neonates, infants, and children to avoid local anesthetic-related systemic toxicity.[148] Suggested pediatric dosing regimens are listed in Table 28.7. Patient-controlled epidural analgesia can be used with continuous infusions of local anesthetic and patient-determined boluses to augment analgesia.[149]

Peripheral Nerve Blockade

Peripheral and truncal nerve blocks have played an increasing role in pediatric postoperative pain management.[131,147,150,151] In addition, these techniques have been described as an effective means of achieving analgesia in the setting of pediatric trauma.[152] Peripheral nerve blocks in children are typically performed under general anesthesia with the use of ultrasound guidance and have a low incidence of complications.[131] Head and neck, truncal, and upper and lower extremity blocks are frequently performed to provide analgesia in suitable candidates.

TABLE 28.7 Pediatric Epidural Dosing Guidelines

Medication	Drug Concentration	Starting Rate	Infusion Limits^
Bupivacaine	0.0625%–0.1%	0.1–0.2 mL/kg/h*	≤0.4 mg/kg/h
Ropivacaine	0.1%–0.2%	0.1–0.2 mL/kg/h*	≤0.4 mg/kg/h
Fentanyl	2–5 µg/mL		0.5–2 µg/kg/h
Morphine	5–10 µg/mL		1–5 µg/kg/h
Hydromorphone	2–5 µg/mL		1–2.5 µg/kg/h
Clonidine	0.5–1 µg/mL		0.5–1 µg/kg/h

*Volume should not exceed 10 mL/h in the thoracic space or 15 mL/h in the lumbar space in pediatric patients.

^Maximum dose should be reduced for thoracic epidurals or in neonates.

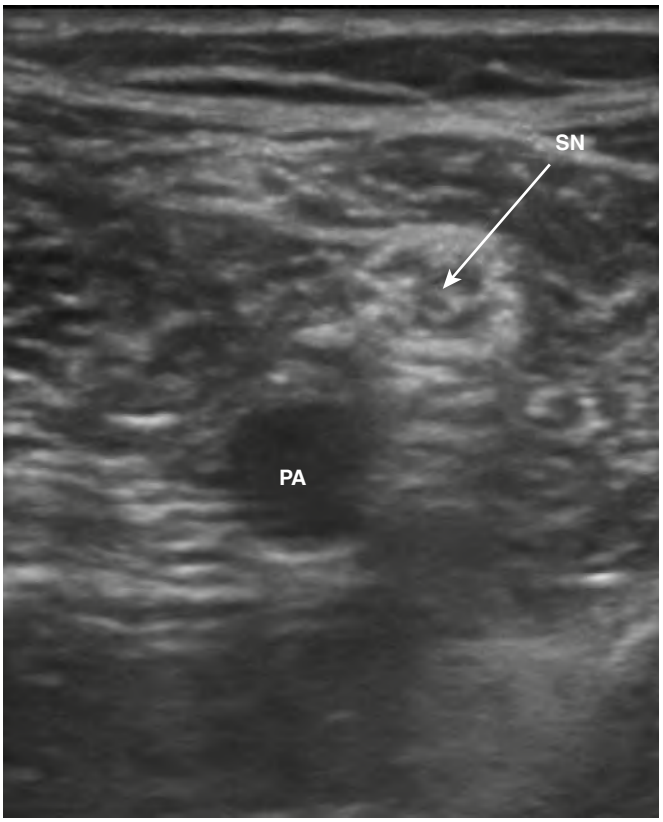
Indications and suggested dosing guidelines for these blocks have been included as a reference point in Table 28.8, although large variability in national dosing practice suggests a need to develop practice guidelines.[153]

Continuous Peripheral Nerve Blockade

Continuous peripheral nerve blocks (CPNBs) placed with ultrasonographic guidance may be used in pediatrics.[154] CPNBs provide effective pain control beyond the 12–16 h typically seen with a single injection block and reduce the need for opioids and their undesirable side effects for multiple days following surgery. CPNBs may be used in the outpatient setting with elastomeric pumps, a relatively inexpensive and easy-to-use method for providing a continuous infusion of local anesthetic with little operator requirement.[155,156]

Two large studies examining thousands of CPNBs placed for postoperative analgesia in children found low rates of failure or complications. The majority of these complications were related to minor catheter malfunction such as dislodgement, occlusion, or leakage.[156,157] Neither of these studies reported any cases with major complications such as neurologic damage, serious infection, or LAST. Superficial signs of infection are more common with catheters that remain in place for greater than three days, consistent with the evidence in the adult literature.[157,158]

The most common indication for CPNBs in pediatric surgical care is for older children undergoing painful orthopedic surgery of a single lower extremity.[156,157] Femoral nerve catheters have been used to facilitate same-day discharge following surgery of the distal femur or anterior knee, such as anterior cruciate ligament reconstruction.[159] Popliteal sciatic catheters for foot and ankle surgery result in fewer adverse effects compared to epidural catheters (Fig. 28.4).[160] Lumbar plexus catheters can provide unilateral analgesia following hip and thigh surgery.



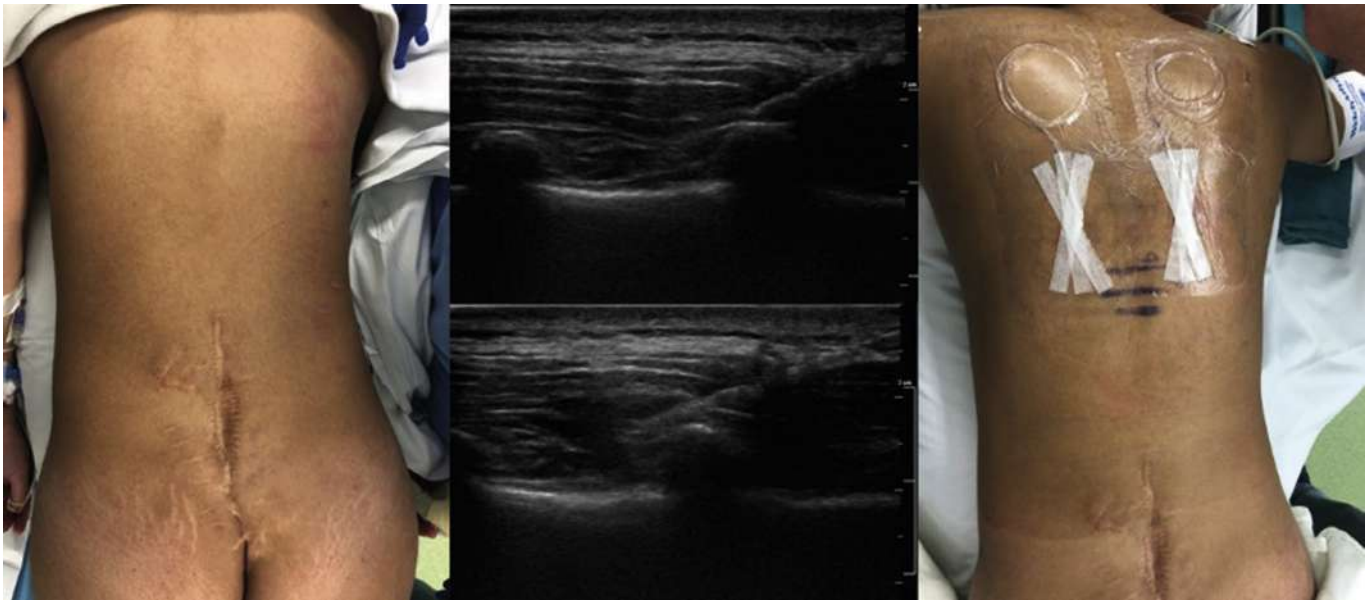
• **Figure 28.4** Sonographic anatomy of the sciatic nerve at the popliteal fossa *(arrow)*. *PA,* Popliteal artery; *SN,* sciatic nerve.

While less commonly used than lower extremity CPNBs, brachial plexus catheters may be used for pain control following upper extremity surgery. Interscalene catheters may be used for shoulder and proximal humerus surgery, such as rotator cuff repair,[161] while supraclavicular, and infraclavicular catheters can provide analgesia following elbow surgery or fracture repair of the radius, ulna, and distal humerus.

One of the most exciting recent advancements in pediatric regional anesthesia has been the introduction of truncal and fascial plane CPNBs, allowing for prolonged analgesia of the thoracic and abdominal walls. Examples include continuous transversus abdominis plane (TAP), paravertebral, and erector spinae plane (ESP) blocks. Compared to epidural catheters, these techniques carry a reduced risk of inadvertent dural puncture, sympathectomy, urinary retention, and neuraxial bleeding or infection and may allow earlier achievement of post-surgical recovery benchmarks such as walking and bladder catheter removal.[127] They may be used when neuraxial

TABLE 28.8 Commonly Performed Peripheral Nerve Blocks in Children With Suggested Dosing Guidelines and Example Indications

Technique	Dose (mL/kg)	Maximum Volume (mL)	Indications
Head and Neck Blocks			
Supraorbital and supratrochlear	0.1–0.15 mL/kg	5 mL	Scalp excision, frontal craniotomy
Occipital	0.1–0.15 mL/kg	5 mL	Scalp excision, occipital craniotomy
Infraorbital	0.1–0.15 mL/kg	5 mL	Nasal surgery, cleft palate/lip repair
Superficial cervical plexus	0.1–0.15 mL/kg	5 mL	Tympanomastoid surgery, cochlear implant
Auriculotemporal	0.1–0.15 mL/kg	5 mL	Tympanomastoid surgery
Suprazygomatic maxillary[167]	0.15 mL/kg	5 mL	Cleft palate/lip repair
Upper Extremity Blocks			
Interscalene	0.1–0.3 mL/kg	15 mL	Shoulder and proximal humerus surgery
Supraclavicular	0.1–0.3 mL/kg	15 mL	Elbow, forearm, hand surgery
Infraclavicular	0.2–0.3 mL/kg	15 mL	Elbow, forearm, hand surgery
Axillary	0.2–0.3 mL/kg	15 mL	Elbow, forearm, hand surgery
Median, radial, ulnar nerves	0.1–0.15 mL/kg	5 mL	Rescue/supplemental analgesia for wrist and hand surgery
Digital nerve	0.05–0.1 mL/kg	2–3 mL	Finger surgery
Lower Extremity Blocks			
Lumbar plexus	0.3–0.5 mL/kg	20 mL	Unilateral hip or proximal leg surgery
Femoral nerve	0.2–0.4 mL/kg	15 mL	Femur shaft fracture, knee surgery, anterior cruciate ligament repair
Adductor canal (saphenous nerve)	0.2–0.4 mL/kg	15 mL	Surgery involving the knee and medial lower leg or ankle
Lateral femoral cutaneous nerve	0.1–0.15 mL/kg	5 mL	Lateral thigh skin graft, muscle biopsy, or hardware removal
Sciatic nerve (intergluteal approach)	0.3–0.5 mL/kg	20 mL	Knee surgery
Sciatic nerve (popliteal approach)	0.3–0.4 mL/kg	15 mL	Knee surgery, foot/ankle surgery
Ankle block	0.1 mL/kg per nerve	1–3 mL per nerve	Polydactyly repair, foot foreign body removal
Trunk and Thorax Blocks			
Intercostal	0.05–0.1 mL/kg	1–3 mL	Thoracotomy, chest tube placement
Ilioinguinal/iliohypogastric	0.2–0.3 mL/kg	15 mL	Inguinal surgery
Rectus sheath	0.2 mL/kg	10 mL	Umbilical and epigastric hernia repair
Paravertebral[168]	0.3–0.5 mL/kg	15 mL	Thoracotomy, pectus excavatum repair
Erector spinae plane[125]	0.3–0.5 mL/kg	20 mL	Thoracotomy, laparotomy, hip surgery
Transversus abdominis plane[169]	0.3–0.5 mL/kg	20 mL	Laparotomy, appendectomy, kidney transplant
Quadratus lumborum[170]	0.3–0.5 mL/kg	20 mL	Lower abdominal, hip, and proximal leg surgery
Penile	0.1 mL/kg	10 mL	Circumcision, meatoplasty
Pudendal[171]	0.3–0.5 mL/kg	5 mL	Hypospadias repair



• **Figure 28.5** Ultrasound-guided placement of bilateral erector spinae plane (ESP) continuous nerve catheters at the T9 transverse processes in a patient with spina bifida undergoing laparotomy.

catheters are contraindicated or difficult to place, such as with spinal dysraphism or in patients with a history of spinal fusion for scoliosis (Fig. 28.5).[162] The location of needle placement for TAP and ESP CPNBs is relatively superficial, far from key structures, and easily compressible. Consequently, these techniques have been used when neuraxial catheters are avoided because of coagulopathy, including in patients undergoing a liver transplant.[163] Finally, while neuraxial catheters are only used for inpatients, truncal CPNBs may be used selectively in the ambulatory setting.[164,165]

Conclusion

The management of acute pain in children presents unique challenges. Specialized assessment tools, behavioral techniques targeted to patient developmental level, recognition of the widespread impact of the opioid epidemic, multimodal analgesic strategies, and increasingly versatile regional anesthesia techniques all play important roles in the optimal care of neonates, infants, and children. Continued advocacy, research, and innovation in this field are imperative to reduce suffering in these vulnerable patients further.

Key Points

- Pain control is necessary to prevent adverse hormonal, metabolic, cardiorespiratory, emotional, and behavioral effects in neonates and young children.
- Various measures of pain intensity are available for the pediatric population, with the selection of the correct scale based on the patient's age, developmental level, and ability to provide feedback.
- Non-opioid analgesics can relieve mild to moderate pain and decrease opioid-related side effects when used as part of a multimodal analgesic strategy for severe pain.
- Children of all ages have been significantly impacted by the opioid epidemic.
- PCA with opioids can be used effectively to control pain and improve patient satisfaction.
- Neuraxial and regional anesthesia techniques provide effective pain relief and can be safely performed under general anesthesia in infants and young children.
- CPNBs provide site-specific analgesia and have certain advantages over epidural catheters.

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29

Low Back Pain Disorders

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Introduction

Musculoskeletal disorders are a common source of pain and disability globally and are ubiquitous in industrialized nations; among them, low back pain (LBP) is the most common.[1] Second only to respiratory tract infections, LBP is the most frequent reason for outpatient doctor visits and, as it often affects the young and the employed, is the most common cause of work related disability.[2] The rising expenditures of LBP, both the direct costs of care and the indirect costs of disability and lost productivity, amount to billions of dollars each year in the United States alone.[3] The reported lifetime incidence of LBP is highly variable, ranging from 13.8%[2] to 31%.[4] This discrepancy is likely because of the poorly defined and heterogeneous causes of LBP. The conditions causing LBP are protean, and the pain can originate not only from the various spinal components and the neural structures housed within the spinal column but also from the surrounding muscles, tendons, and ligaments. Additionally, pain can be referred from the abdominal and pelvic viscera and the adjacent joints. Thus the list of structures causing LBP is extensive and includes the intervertebral discs (IVDs), vertebral bodies, facet joints, spinal nerve roots (NRs), the spinal and paraspinal soft tissues, and the sacroiliac and hip joints. This unwieldy list of possible etiologies of LBP can be initially managed by categorizing these conditions into two broad groups: a) conditions that, if untreated, can be life threatening or can cause serious neurologic injury and b) conditions that are benign and self-limiting and are unlikely to cause neural damage.[5] The first group is typically comprised of *fractures and dislocations* of the spine, both primary and secondary; *tumors and infections* of the spinal and related neural structures; *inflammatory conditions* such as ankylosing spondylitis and rheumatoid arthritis; *metabolic conditions* such as Paget's disease; and *spinal deformities* such as scoliosis and kyphosis. The second category of spinal pain generators consists of a wide range of benign and self-limiting conditions that includes lumbar sprain and strain, myofascial pain syndrome (MFPS), herniated disc (HD), lumbar spinal stenosis (LSS), degenerative disc disease (DDD), internal disc disruption (IDD), lumbar facet syndrome (LFS), sacroiliac joint dysfunction (SIJD), spondylolysis, spondylolisthesis, and spinal instability (SI). In this book, we discuss the causes of LBP pertinent to the practice of pain medicine. This specific chapter discusses conditions causing LBP that can be linked to the dysfunction of the IVDs (DD) and include HD, LSS, DDD, IDD, and LFS. Other significant causes of LBP, e.g. pain of muscular and ligamentous origin, MFPS, SIJD, and SI, though associated with DD, frequently occur independently and are discussed elsewhere in this textbook. Conditions that are life threatening or can cause serious neurologic compromise, that is, the first group, are generally ruled out prior to a referral to a pain medicine physician and are beyond the scope of this chapter. LBP frequently radiates to the lower extremities either in dermatomal (radicular pain) or non-dermatomal (referred pain) distribution, and a brief discussion of both categories will be presented.

Lumbar Radicular Syndrome

Definition and Terminology

Pain, paresthesia, and numbness in a dermatomal distribution and a positive straight-leg raise (SLR) test, with or without accompanying signs of sensory loss, weakness, and diminished reflexes, are mediated by sensory spinal NRs (SSNRs) or dorsal root ganglia (DRG).[6] These symptoms of lumbar radicular syndrome (LRS) can be present in isolation. However, they are generally present in conjunction with LBP. The incidence of LRS in patients with LBP is reported to range from 12% to 40%.[2] Other terms used for LRS include *lumbar radiculopathy*, which inappropriately implies the presence of objective signs of NR damage-loss of sensation, muscle weakness, and diminished reflexes; *lumbar radiculitis,* which incorrectly proposes that an inflammatory process is primarily responsible for the radicular signs and symptoms; and *lumbar radicular pain*, which mistakenly assumes that pain is always the principal symptom. Hence, the descriptive term *LRS* may be the most accurate as it correctly suggests a constellation of clinical signs and symptoms of variable etiology secondary to the pathology or dysfunction of the SSNRs or DRGs. The term *sciatica* is also often used synonymously with LRS. However, this term incorrectly implies that the level of injury is at the peripheral nerve rather than the SSNR or DRG. Because of convergence and overlap of somatosensory input at the spinal and supra-spinal levels, pain from the various low back pathologies, e.g. IDD, FJS, SIJD, can refer to the lower extremities without the involvement of SSNRs or DRGs. This pain is non-dermatomal in distribution and typically radiates to the buttocks and lateral thighs; it rarely radiates below the knee joints into the legs and feet.

Etiology and Differential Diagnosis

LRS is caused when the impulses generated at the SSNR and DRG locations are perceived as pain, numbness, or tingling in areas innervated by the affected axons, i.e. in a dermatomal distribution (Fig. 29.1).[6] The pathologic processes causing LBP and LRS are similar, but there is obligatory involvement of SSNRs and DRG in LRS. Lesions in the IVD and spinal stenosis are the most common cause of LRS. Additionally, neoplastic, infectious, traumatic, metabolic, and vascular lesions discussed can also involve the SSNRs, DRGs, and the lumbosacral plexuses and can infrequently produce radicular signs and symptoms.[7] The entrapment neuropathies involving the sciatic nerve (e.g. the piriformis muscle and the ischial tunnel syndromes) can also generate pain and paresthesia in the lower extremity. However, these typically affect multiple dermatomes.[7] The somatic referred pain, because of interneuronal convergence within the spinal cord, in addition to being non-dermatomal in nature, has a deep aching quality and lacks the objective signs of NR involvement.

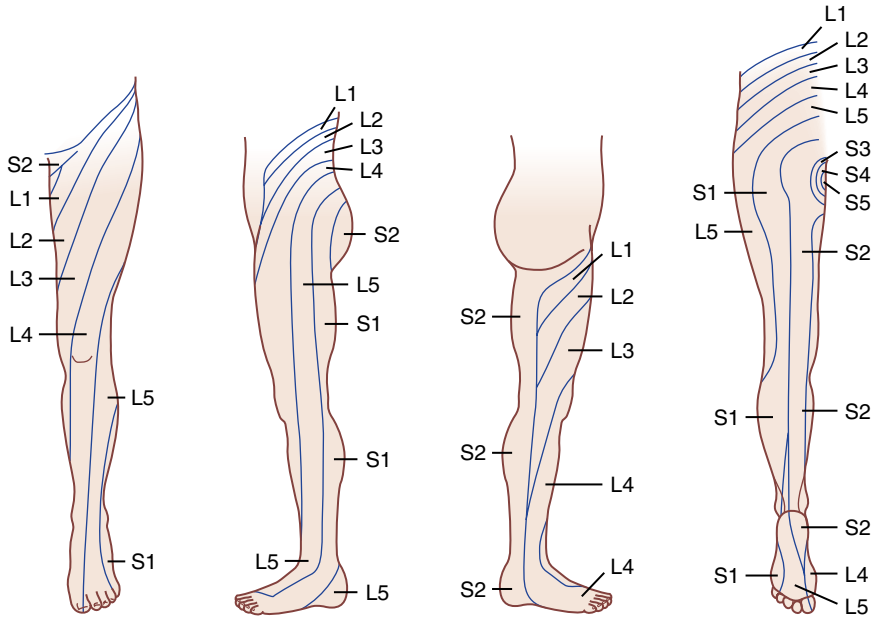
Clinical Features

Though pain is the predominant symptom, other features of radicular involvement include paresthesia, numbness, and weakness in the distribution of the involved NR. Radicular pain typically travels along a narrow band and is of sharp, shooting, and lancinating quality.[8] Objective signs include gait disturbances, loss of sensation, reduced muscle strength, and diminished reflexes involving the corresponding dermatome. HDs and the degenerative spinal conditions typically involve the lower lumbar NRs, whereas the more sinister causes of LRS, e.g. local tumor invasion, tend to involve more superior NRs with greater frequency.[9] Characteristic features of the various lumbar and sacral NR involvement include:

- S1: Pain, paresthesia, and numbness of the posterior part of the thigh, calf, and plantar surface of the foot, difficulty toe walking, weakness of plantar flexion, and loss of the plantar reflex.
- L5: Pain, paresthesia, and numbness involving the buttock, anterolateral aspect of the leg, dorsal surface of the foot and great toe, difficulty heel walking (steppage gait), and weakness of ankle and toe extension.
- L4: Pain, paresthesia, and numbness involving the anterior part of the thigh, knee, and upper medial portion of the leg, weakness of knee extension, and a diminished patellar tendon reflex.
- L3 and L2: Pain, paresthesia, and numbness involving the groin and inner thigh areas, weakness in hip flexion.
- Lower Sacral NRs: Decreased sensation in the buttock and perineal areas (i.e. saddle anesthesia) and autonomic dysfunction as indicated by bowel and bladder dysfunction (typically urinary retention and constipation followed by incontinence), and sexual dysfunction manifested as loss of erection in men and vaginal anesthesia in women.[10,11]

Clinical Tests of Nerve Root Irritation

Several tests can be performed to confirm the presence of NR irritation (Box 29.1). Passive SLR test or Lasègue test assesses the presence of worsening pain in the radicular distribution with ankle dorsiflexion of the extended lower extremity, which results from the traction of lower lumbar NRs that are drawn caudally between 1.4 and 4 mm.[12] Therefore a positive SLR suggests radicular pathology of the lower lumbar NRs (L4, L5, and S1). Radicular pain in the affected leg when the contralateral asymptomatic leg is similarly raised constitutes an X-SLR test. Although a positive SLR test is highly sensitive, X-SLR is more specific for lumbar NR irritation.[13] An increase in back pain during SLR is typically attributed to NR movement in lumbar spinal segments,[14] and a centrally HD can exclusively generate LBP with an SLR because of strain on the anterior theca.[15] Tripod test confirms positive SLR test in a patient in sitting position—with the patient seated, the knee is extended and the foot dorsiflexed. During a femoral stretch test, the patient is in a prone position, the knee is flexed, and the hip extended; it places the L2 and L3 NRs under tension and indicates irritation of these NRs.



• **Figure 29.1** Lower extremity dermatomes.

• BOX 29.1 Tests to Confirm the Presence of Nerve Root Irritation

Straight-leg raise
Straight-leg raise and ankle dorsiflexion of the extended lower extremity
Crossed straight-leg raise
Tripod test
Femoral stretch test

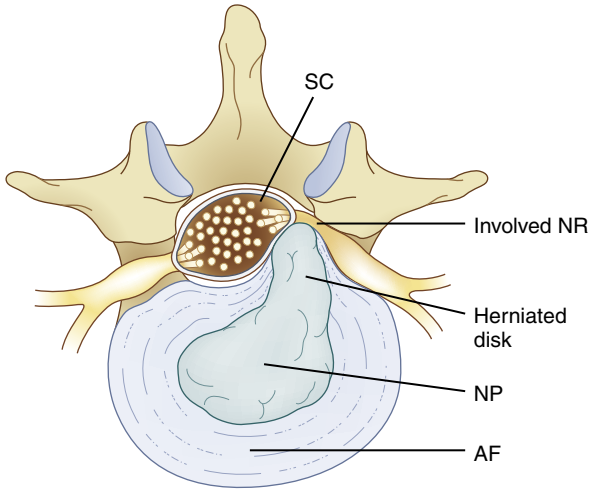
Lumbar Herniated Disc

History and Epidemiology

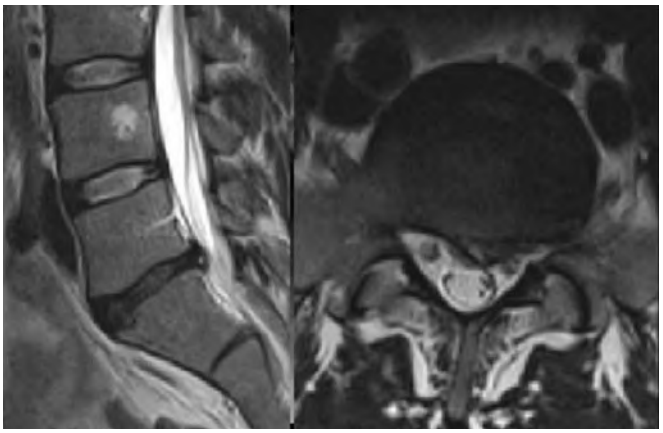
Although radicular symptoms have been known since ancient times, they were first attributed to "posterior displacement of the disc" by Goldthwaite in 1911.[16] The incidence of symptomatic HD is estimated to be 1% to 2% in the general population, for which approximately 200,000 lumbar discectomies are performed each year.[17]

Terminology

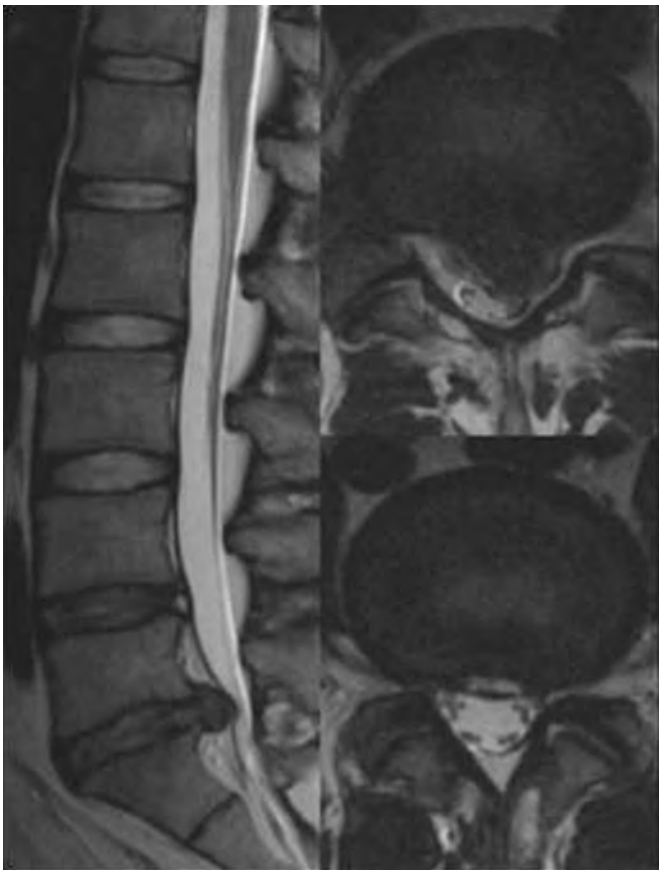
Disc herniation may be defined as the displacement of disc material beyond the confines of the IVD space (Fig. 29.2).[18] Although the nucleus pulposus (NP) is typically the principal component, other constituents (e.g. cartilage, bone, and disc annular tissue) also frequently comprise the HD material.[19] The various terms used to describe disc herniation include *herniated NP*, *ruptured disc*, *prolapsed disc*. However, the term *HD* seems most appropriate as it conveys the concept of displacement of any disc component regardless of source. HD is further classified based on the morphology of the herniated material.[18] A *protruded disc* is present when the neck (i.e. the distance between the edges of the base) of the herniated material is wider than the widest disc diameter in any given plane (Fig. 29.3). *Disc extrusion* is the opposite of disc protrusion in that the neck is narrower than the widest disc diameter in any given plane (Fig. 29.4). *Disc sequestration* is a type of disc extrusion whereby no continuity exists between the herniated material and the parent disc. HD is also classified based on the integrity of the overlying annulus fibrosus (AF). A *contained* herniation, in contrast to a *non-contained* herniation, is distinguished by the fact that the displaced disc material is covered by an intact annulus. Of note, the currently available diagnostic modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and discography, are unable to accurately ascertain the integrity of the disc annulus, and these distinctions may be arbitrary. The terms *desiccation*, *fibrosis*, *narrowing*, *bulging*, *fissuring*, and *sclerosis* of the disc are also used. However,



• Figure 29.2 Schematic depiction of disk herniation. *AF*, Annulus fibrosus; *NP*, nucleus pulposus; *NR*, nerve root; *SC*, spinal cord.



• Figure 29.3 T2-weighted sagittal and axial magnetic resonance images of disk protrusion.



• Figure 29.4 T2-weighted sagittal magnetic resonance images of a 31-year-old man with severe axial and lower extremity pain showing two distinct disk pathologies. At the L5-S1 level, there is left-sided disk extrusion, and the L4-5 disk shows desiccation and a high-intensity zone; the remaining disks appear normal.

they suggest degenerative disc processes and do not reflect disc herniation.[18]

Pathophysiology

Since Mixter and Barr first reported alleviation of radicular symptoms after removal of herniated disc material in 1934, HD is thought to be the most common cause of LRS.[20] Data from animal studies indicate that NR compression impairs nutrition and can cause ischemic injury,[21,22] and deformation of the affected NR by HD fragments are often evident on diagnostic imaging studies in human patients with radicular symptoms.[23] Therefore mechanical compression of the NRs by the herniated disc material (see Fig. 29.2) has been commonly acknowledged as the preeminent source of LRS. However, clinical studies have shown that NRs exposed to mechanical deformation and HD material for prolonged periods produced pain while similar NR deformation without exposure to HD material caused no pain.[23] Furthermore, HD material retrieved from patients at the time of discectomy has demonstrated the presence of inflammatory mediators,[24,25] and in animal models, the application of the NP, and not the epidural fat, to the NR produced physiologic and anatomic evidence of radiculopathy.[26] The presence of clinical and electromyographic evidence of LRS has also been demonstrated in patients with normal findings and no pressure effects on spinal imaging.[27] Taken together, these observations suggest that inflammatory mediators and inflammation rather than mechanical compression play a central role in LRS because of HD.

Natural History

The natural history of HD is favorable, and most patients (over 60%) experience significant improvement in their symptoms within the first few months. However, a substantial minority (between 20% to 30%) will fail to improve.[28] Clinical improvement is usually accompanied by resolution of HD on spinal imaging.[29] Large extruded discs decrease in size more rapidly and with greater frequency than smaller disc protrusions and bulges.[30] Physiologic regression of the HD is thought to be via phagocytic processing by macrophages, which are more prevalent in the outermost layers of HD material.[31] Therefore the paradox of larger herniations diminishing more rapidly can be explained by the greater surface area available for phagocytosis in a large extruded disc.

Clinical Correlations

Most lumbar disc herniations occur at the lower lumbar levels, with the L4/5-disc level being the most common (59%), followed by the L5/S1 (30%) and L3/4 (9%) disc levels.[32] Herniation at these levels produces typical radicular signs and symptoms in the affected dermatomes, while centrally HDs may primarily cause LBP with both being exacerbated by SLR.[15] Large, often central, disc herniations can cause neurologic compromise and cauda equina syndrome (CES).

Cauda Equina Syndrome

CES is caused by compression, typically acute compression, of the spinal NRs comprising the cauda equina in the lumbosacral spine. The overall incidence of CES is low, affecting approximately 4/10,000 patients with LBP.[33] CES is most frequently caused by a massive midline disc herniation,[10,11] or smaller disc herniation in a previously stenotic spine.[10,11] Rare causes of CES include spinal metastases, hematoma, epidural abscess, traumatic compression, acute transverse myelitis, and abdominal aortic dissection. Almost 70% of patients with CES also have a history of chronic LBP, but CES is the primary complaint in the remaining 30% of the affected population.[32] These patients, typically seen within 24 h of the onset of their symptoms (Box 29.2), usually present with bilateral but often asymmetric lumbar radicular pain (LRP) and less frequently with LBP. The pain is often accompanied by weakness in both feet, gait disturbances (secondary to pain and weakness), abdominal discomfort (because of urinary retention), urinary overflow incontinence, or bowel incontinence. Objective signs include motor and sensory deficits, diminished reflexes, and positive SLR test, often present in lower extremities. Symptoms of particular significance are diminished sensation in the buttocks and perineum (saddle anesthesia), diminished sphincter tone, and evidence of urinary bladder retention on examination. In approximately 10% of patients with signs and symptoms suggestive of CES, the cause is compression of the spinal cord at more superior levels, i.e. at the thoracic or even the cervical spinal cord.[34] These patients have weakness of the lower extremities, similar to lesions at lower spinal levels, but experience higher levels of sensory loss, corresponding to the level of spinal cord involvement, and may have increased tone and reflexes in the lower extremities.[35] MRI is the "gold standard" for diagnosis of CES, and imaging of the entire spine (lumbar, thoracic, and cervical) is often performed because of the possibility of spinal cord compression at higher levels.[34,35] Once the diagnosis is made, treatment involves high dose intravenous steroids and urgent decompressive surgery to reduce permanent neurologic injury and resulting disability.[32]

• BOX 29.2 Clinical Signs and Symptoms of Cauda Equina Syndrome

Features in the Clinical History

Radicular pain in both lower extremities; pain in one leg may be greater
Isolated low back pain is rare
Complaint of weakness in one or both legs and feet
Gait disturbances because of pain and weakness
Abdominal discomfort as a result of urinary retention

Features in the Clinical Examination

Motor and sensory deficits in the lower extremities
Diminished lower extremity reflexes
Positive straight-leg raise and crossed straight-leg raise tests
Saddle anesthesia
Diminished sphincter tone
Evidence of urinary bladder retention

Treatments for Herniated Discs

Because of the favorable natural history, herniated discs are typically managed expectantly with symptomatic treatment in the absence of neurologic deficits.[35,36] Other specific treatments for HD include a variety of injections and minimally invasive or larger-scale surgical interventions.

Injections for Herniated Disc

Epidural steroid injections (ESIs) have been used to treat HDs for more than 50 years. Traditionally, a posterior interlaminar (IL-ESI) approach is used, and the injectate reaches the anterior

• BOX 29.3 Predictors of Favorable Outcomes of Conservative Noninvasive Treatment of Herniated Disks

Negative crossed straight-leg raise test
Absence of leg pain on extension of the spine
Return of neurologic function within 12 weeks of onset
Absence of stenosis on spine imaging
Favorable response to epidural steroid injections
Patient with 12 years of education
Motivated and otherwise healthy patient
Absence of comorbid psychologic condition
Absence of workers' compensation claim

portion of the spinal canal near the HD by flowing through the circumferential epidural space around the thecal sac. Transforaminal epidural steroid injections (TF-ESIs) have the theoretical advantage of delivering the injectate directly to the anterior epidural space. Fluoroscopic guidance can improve the precision with which the injectate is deposited in the epidural space.[37] The literature is replete with case series and uncontrolled studies, both in support of and against the efficacy of ESIs. However, a review of the randomized controlled trials (RCTs) of IL-ESI for LRP show ESIs to be more beneficial than control treatments, particularly in the short term, and TF-ESIs were found to be superior to IL-ESIs.[38,39] ESIs are discussed in detail in Chapter 65.

Predictors of Outcome with Expectant and Non-invasive Treatments for HD: Predictors of a favorable outcome from conservative treatments include 1) a negative X-SLR test; 2) absence of leg pain with spine extension; 3) absence of degenerative disc changes on spinal imaging; 4) favorable response to ESIs; 5) resolution of any neurologic deficits within 12 weeks; 6) a motivated, otherwise healthy patient; 7) more than 12 years of education; 8) absence of workers' compensation claims, and 9) absence of comorbid psychologic disorder (Box. 29.3).[40]

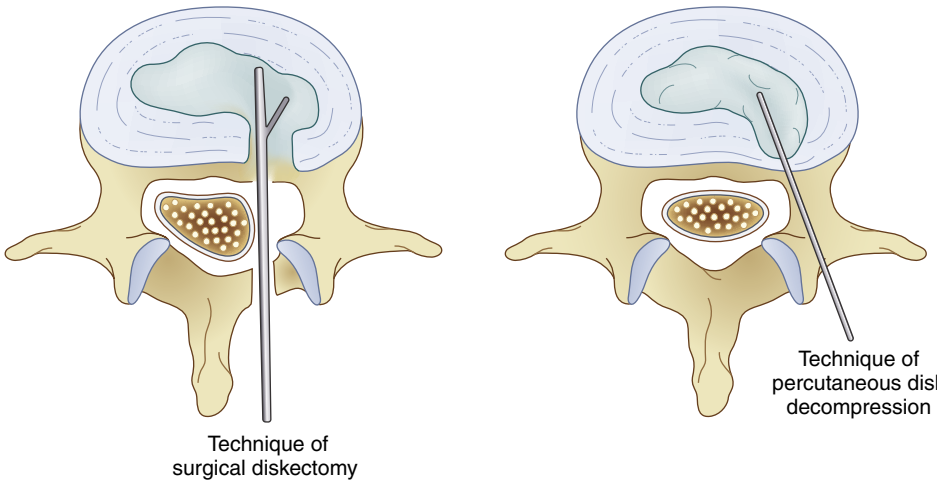
Minimally Invasive Treatments for Herniated Discs

Percutaneous disc decompression (PDD) was developed following the success of intradiscal injection of chymopapain for LRP from an HD. Positive results of the intradiscal chymopapain injections suggested that the dissolution of non-herniated intranuclear disc contents may resolve the HD symptoms without directly targeting the HD material (Fig. 29.5). However, chymopapain injections are rarely performed in the United States because of the complications of unintentional injection of this substance into the subarachnoid space and the rare occurrence of severe allergic reactions. During PDD, non-herniated NP tissue is removed, which is postulated to reduce intradiscal pressure that allows inward collapse of the HD fragment. This therapeutic intervention is likely effective in the presence of an intact AF, i.e. when the herniation is assumed to be contained, presumably when the HD fragment is smaller than 4 mm.[41] Based on the principles of joint endoscopy, PDD was initially conducted by using large-bore endoscopes, 7 mm or greater in internal diameter, which were used to remove the NP material. However, these early endoscopes were cumbersome to operate and had the added risk of trauma to the disc annulus and, hence, were quickly abandoned. The technique of automated percutaneous lumbar discectomy (APLD) used a smaller introducer cannula (2.5 mm in internal diameter), and the nuclear material was removed with a suction and cutting technique. Later, a variety of lasers were used to vaporize the nuclear material. These laser disc decompression devices had smaller cannulas, less than 3 mm in internal diameter, and often included a fiberoptic channel for observation. The technique of disc Nucleoplasty® used a smaller (1.5 mm, 17 gauge) introducer needle and bipolar radiofrequency (RF) energy to create small channels, removing the nuclear material. A percutaneous discectomy technique with the proprietary name of DeKompressor® uses 1.5 and 1.0 mm (19 gauge) outer cannulas and a probe that rotates to remove the disc material. A modified intradiscal electrothermal therapy (IDET) catheter (Acutherm®) aimed to induce localized thermal lesioning and shrinkage at the base of the HD material.

Despite its use spanning several decades, evidence supporting the use of the various PDD techniques is lacking. In one study, MRI of patients before and after APLD showed no difference in the size of HDs at six weeks.[42] Although animal[43] and cadaver studies[44] have shown a reduction in disc pressure after PDD. No evidence exists of high intradiscal pressure in patients with HDs, or its reduction after PDD procedures. Furthermore, the amount of nuclear material removed is variable for the various PDD techniques, ranging from 4 to 5 gm for APLD, 1 gm for Nucleoplasty® and DeKompressor® devices, variable for the various laser procedures, and unknown for the Acutherm® device. Removing large amounts of disc material has been linked to disc collapse and accelerated disc degeneration.[45] However, studies correlating disc pressure and outcomes with a specific amount of nuclear material removed suggest that the optimum amount of disc material that should be removed is unknown. Therefore it may be prudent to remove the least amount of disc material possible to achieve the most beneficial results. Similarly, the use of smaller-gauge introducer cannulas would limit the annular damage and should be preferentially used. Removing nuclear contents from within the disc protrusion itself via a more lateral percutaneous approach has also been suggested.[41] Discography followed by a post-discography CT scan to assess the size and location of the HD and the integrity of the disc annulus has also been proposed prior to the PDD. This practice has been linked to improved outcomes.[46] Two RCTs of APLD showed success rates of 29%[47] and 33%.[48] However, no such trials support the use of laser disk decompression, Nucleoplasty®, DeKompressor®, and Acutherm®, and their use remains anecdotal.

Operative Treatments for Herniated Discs

A detailed discussion of the various surgical procedures for HD is beyond the scope of this chapter. Classic discectomy, first popularized by Mixter and Barr in 1934,[20] is the most popular procedure performed for HD. This technique fundamentally includes laminectomy and release of ligamentum flavum to access the epidural space, removal of the HD fragment, and annulotomy to remove the non-herniated disc material (see Fig. 29.5). Several variations of this technique exist, which differ in the extent of laminectomy and ligamentum flavum release and annulotomy performed during the procedure. The micro-discectomy procedure is less invasive and aims to minimize the surgical trauma and limit the potential for NR injury and epidural scarring. Although surgery is commonly performed for HD,[17] little high-quality evidence exists in its support. A prospective trial comparing surgical and non-surgical treatments for HD showed superior outcomes in surgically treated (92%) than the nonsurgically treated patients (61%) at one year.[49] However, these results deteriorated over time, with differences between the groups becoming less significant at four years and insignificant at ten years. This study was also criticized for lacking careful randomization and blinding, a large crossover



• **Figure 29.5** Schematic depiction of surgical discectomy and percutaneous disk decompression.

of patients to the surgical group, insensitive outcome measures, and small sample size.[50] Another frequently cited study in support of operative treatments is a non-randomized and observational study with similar results at one and five years but slightly favorable results for surgical treatment at ten years (56% vs. 40%, $P = 0.006$).[51] The spine patient outcomes research trial (SPORT)[52] showed primary outcomes to be in favor of surgery at all observation periods. However, these differences were not statistically significant, and the main benefit of the surgery was the faster resolution of pain. It appears that the main reason to undergo surgery is the urgency with which a patient wishes to achieve pain relief over the following two to four months.[53] However, the need for surgery is absolute in patients with CES,[32] and surgical treatment is generally necessary for patients with progressive motor deficits. In contrast, other indications for surgery, including intractable pain and poor response to conservative therapy, appear relative.[54] The results of micro-discectomy have been reported to be superior to those of traditional discectomy.[56] Although patients with "sciatica" of more than 12 months duration have been shown to have less favorable results after surgery,[57] the full effects of a potential delay in operative treatment, while nonsurgical treatment is attempted, remain unknown. Overall, the lack of consensus and variability of adherence to indications for surgery is demonstrated by the nearly 20 fold difference in surgery rates in otherwise demographically similar United States populations.[55]

Lumbar Spinal Stenosis

Terminology and Etiology

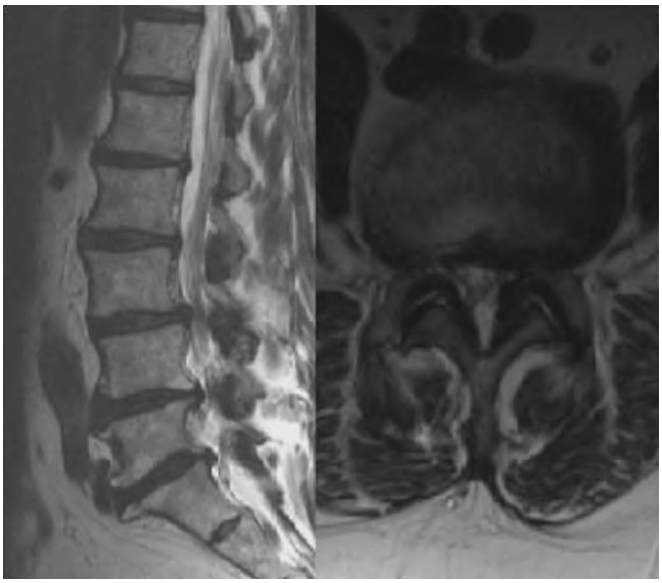
LSS is defined as the clinical syndrome of neurogenic claudication or radicular symptoms from narrowing of the spinal canal, neuroforaminae, and/or lateral recess generally assumed to be from compression of the neural elements.[58] Though LSS has been recognized for some time, its modern descriptions first appeared in medical literature in 1954.[57] LSS is typically classified (Table 29.1) into congenital and acquired varieties, with the latter being the most common. Congenital or developmental LSS is generally idiopathic in nature but rarely can be from developmental bone dysplasia such as achondroplasia. Acquired LSS is most frequently degenerative in nature, and the less common causes include metabolic disorders such as Paget's disease, trauma, surgery, spinal tumors, and spinal deformities. LSS has also been classified by anatomic criteria into central stenosis because of narrowing of the spinal canal and lateral stenosis because of narrowed neural for aminae and/or lateral recess.[58]

Pathophysiology

The most common, the acquired degenerative variety, of LSS is characteristically because of disc degeneration and its sequelae. The typical lesions include 1) loss of disc height, 2) AF bulging, 3) facet joint hypertrophy, 4) thickening and redundancy of the ligamentum flavum, and 5) local osteophyte formation.[59] Therefore the stenotic changes are typically at the level of the IVDs, and one or several vertebral motion segments may be involved (Fig. 29.6). Central stenosis can cause compression of the NRs of the cauda equina, whereas lateral stenosis typically results in compression of the exiting spinal NRs. The L5 NR is most commonly involved (75%), followed by the L4 (15%), L3 (5.3%), and L2 (4%) NRs.[60] The capacity of the lumbar spinal canal is significantly greater during flexion and reduced during extension. Therefore the symptoms of LSS are typically worse during lumbar extension.[61] Notwithstanding, degenerative changes of LSS are prevalent in older adults[62] and are frequently also seen in asymptomatic individuals.[36] Direct

TABLE 29.1 Classification of Lumbar Spinal Stenosis

Etiologic Classification	
Congenital	Idiopathic
	Achondroplastic
Acquired	Degenerative
	Iatrogenic-postsurgical
	Metabolic-Paget's disease
	Post-traumatic
	Deformity-spondylolisthesis
Combined	Congenital with secondary degenerative changes
Anatomic Classification	
Central stenosis	Central spinal canal stenosis
Lateral stenosis	Lateral recess stenosis
	Neural foraminal stenosis



• **Figure 29.6** T2-weighted sagittal and axial magnetic resonance images of multilevel lumbar spinal stenosis.

compression and/or ischemia of the neural structures is generally thought to be responsible for the clinical manifestations, and in contrast to HD, the role played by the inflammatory changes is less clear.[63] The degenerative changes that result in spinal stenosis can also give rise to SI, degenerative spondylolisthesis, and spinal deformities, including degenerative scoliosis, which can further exacerbate spinal narrowing.

Clinical Considerations

- *Neurogenic claudication*: The typical manifestations of neurogenic claudication include pain radiating to both lower extremities—posterolateral aspect of the thighs and legs—which is exacerbated with standing, walking, and lumbar extension and is relieved by sitting. The pain is often associated with numbness and heaviness or weakness of the lower extremities. These symptoms must be distinguished from claudication of vascular origin, and this possibility should be entertained in the presence of signs related to vascular insufficiency.[64] In contrast to vascular claudication, the pain of neurogenic claudication can be present with standing only and can be eased by walking in a flexed position, such as leaning on a walker or shopping cart.[65]
- *Radicular pain*: Radicular symptoms unrelated to any activity can be a sign of NR involvement. This usually reflects lateral stenosis and can be present with or without symptoms of neurogenic claudication.[66]
- *Axial pain*: Axial pain is more reflective of disc, facet joint, or sacroiliac joint pathology. It may indicate SI and is unlikely to be the leading feature of LSS.[67]
- *Clinical signs*: Patients with LSS tend to walk with a forward flexed gait and often maintain this "stooped posture" position while standing with the loss of lumbar lordosis and decreased range of lumbar extension. Because of the slow and chronic nature of the progression of LSS, the SLR test is infrequently positive, and the sensorimotor deficits are less pronounced. In a study of patients with LSS, a sensorimotor deficit in the lower extremity was seen in 30% of patients (most commonly in the L5 NR distribution), a decreased or absent plantar reflex was present in 43%, and a diminished patellar reflex was noted in 18% of the patients; the SLR test is positive in only 10%–23% of patients.[68]

Natural History and Treatment Options

Even though LSS was initially thought to be unrelentingly progressive,[70] its natural history can be defined by intermittent pain flares, or it may remain relatively unchanged over time.[71,72] Because of its seemingly progressive nature and poor prognosis, LSS was treated in the past with early surgical interventions.[70] However, nonsurgical treatments have been shown to effectively control the symptoms.[72,73] Surgical treatment of LSS typically provides superior control of the symptoms initially,[74] but the benefits seem to decline over time.[75] The prevalence of this condition in older adults and the frequent presence of other comorbid conditions often make these patients unsuitable for major surgical intervention. Moreover, delaying surgery for a trial of nonsurgical treatment, even with severe stenosis, has been shown to have minimal detrimental effect on the final surgical outcomes.[76] Therefore in the absence of progressive neurologic deficits or CES (rare in spinal stenosis), nonsurgical treatments are prudent, and surgery should be reserved for patients who have failed appropriate trial of non-operative therapies.

Non-operative Treatments

Non-operative treatments for LSS, including medications, activity modification, bracing, and physical therapy, are discussed later in the chapter. ESIs, particularly IL-ESIs, are effective in the short term treatment of acute pain exacerbations and can provide symptomatic control of episodically worsening symptoms of neurogenic claudication.[77] Fluoroscopically guided TF-ESIs appears to be a treatment better suited for radicular symptoms secondary to LSS and have been shown to have both short term and long-term efficacy.[78,79]

Operative Treatments

Wide laminectomy performed at the stenotic levels is the standard procedure for surgical decompression of LSS.[80] It involves broad removal of the spinal laminae and ligamentum flavum extending laterally from pedicle to pedicle. Extensive removal of the posterior spinal elements can result in SI, which can be avoided by the preservation of the pars interarticularis and the lateral halves of the facet joints. Extensive decompressive surgery, typically performed for complex stenosis and degenerative spondylolisthesis, may result in significant SI. The post-decompressive instability may be avoided by fusion performed with or without instrumentation.[80] The various approaches to lumbar decompression and fusion have included the traditional posterior lumbar inter-body fusion (PLIF) and, more recently, anterior lumbar inter-body fusion (ALIF), lateral lumbar inter-body fusion (LLIF), and transforaminal lumbar inter-body fusion (TLIF).[81] These approaches are frequently combined, and the anterior and lateral approaches (LLIF and TLIF) can reduce the amount of surgical muscle dissection and minimize the nerve manipulation required to access the vertebrae, discs, and nerves. Lately, surgical techniques involving minimal decompression, such as laminotomy, fenestration, and laminoplasty, are increasingly used to preserve spinal stability and avoid post-decompressive fusion.[82] However, these minimally

decompressive techniques can be accompanied by higher rates of restenosis.

Degenerative Disc Disease

Lumbar disc degenerative changes most clearly seen on magnetic resonance (MR) imaging include 1) disc desiccation; 2) reduced disc height; and 3) disc bulging. Often referred to as DDD, these changes are frequently linked to LBP; however, they are also considered age-related physiologic variants.[83] To further comprehend DDD one must first understand the basic disc anatomy, physiology, and age-related changes in the disc.

Anatomy and Physiology of the Intervertebral Disc

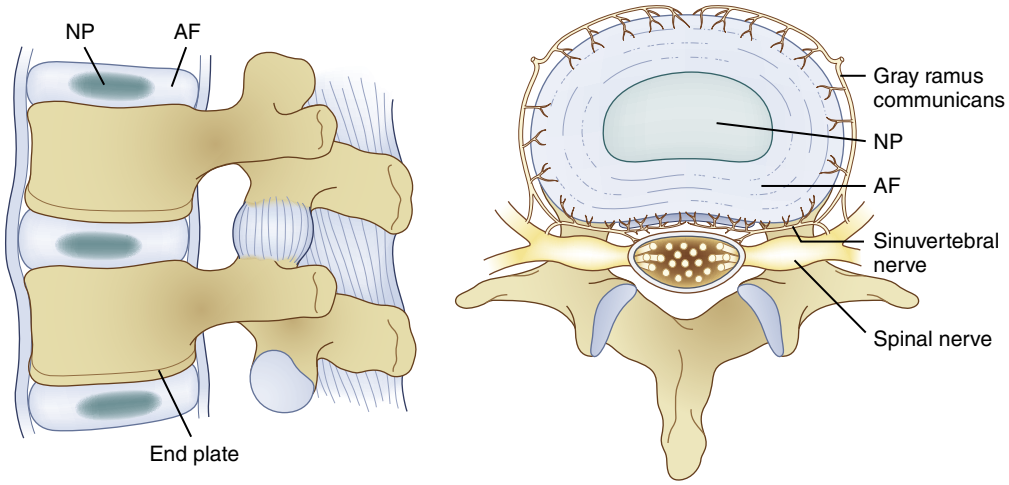
Healthy IVDs are an integral component of the spinal column as their collective plasticity engenders spinal flexibility that is vital to the agility enjoyed by vertebrates. The IVD is a doughnut shaped structure interposed between the adjacent vertebral bodies and can be grossly compartmentalized into an outer rim, the AF, the inner NP, and the cartilaginous endplates (Fig. 29.7). This distinction, most obvious at the lumbar levels, decreases with advancing age. Both NP and AF are sparsely populated by cells of variable origin that maintain the disc function and integrity. The NP is inhabited by chondrocyte-like cells found in clusters, whereas AF is populated by fibrocyte-like cells.[84] The abundant intercellular disc matrix is different for the NP and AF. In the NP, the matrix is jelly-like and has a high concentration of water and proteoglycans, whereas in the AF, the matrix is firmer and has high collagen content. The collagen fibers in the AF are arranged as interlacing lamellae, which are firmly attached to the adjacent vertebral bodies.[84] Due to their central pivotal position, the IVDs are exposed to intense compressive forces that can vary instantaneously, with postural changes and weight bearing, from negative to extreme positive pressures. However, a healthy IVD is strikingly resilient, transcending the adjoining vertebral bodies, as it maintains the critical gap between the adjacent vertebral bodies and relieves the loading stress on the contiguous structures, i.e. the spinal ligaments and the facet joints.[85] These axial compressive loading forces are borne directly by the NP, which because of its inelasticity, are dispersed as the lateral stretch of the tensile AF collagen fibers.[86] The incompressibility exhibited by the NP is largely because of its high water content, which is maintained in turn by the hydrostatic pressure generated by its high proteoglycan content.[84] Apposite NP proteoglycan concentration is maintained by a delicate balance between the anabolic activities of the NP cells and the enzymatic activities of NP matrix metalloproteinases (MMPs).[87] The IVD is largely avascular, and the metabolic requirements of cells in NP and AF are met almost exclusively by diffusion to and from capillary plexuses located in the outer AF and the adjacent vertebral bodies across the avascular cartilaginous end plates.[88] This arrangement is tenuous at best, and the disc cells, especially in the NP, function in a precarious anaerobic environment.[89] The IVD also lacks scavenger cells, and the degradative products of disc macromolecules, therefore, accumulate over time and alter the normal cell and matrix interactions.[90] Therefore the state of hydration, the compressibility of the NP, and the disc itself can be altered by a host of factors influencing metabolic activities within the disc.

Vascularity and Innervation of the Intervertebral Disc

IVD is the largest avascular structure in the body and is also scantly innervated. The vascularity and innervation in a normal IVD are limited to the outer one-third of the AF, and the NP lacks completely any blood supply and innervation.[84,91] Innervation of the outer third of the AF, mainly mechanoreceptors, is by plexuses along the anterior and posterior longitudinal ligaments (see Fig. 29.7).[92] The posterior plexus receives its input from the sinuvertebral nerve and the gray rami communicans, the latter also contributing to the anterior plexus. The sinuvertebral nerve receives its contributions from the ventral rami and the gray rami communicans.[92] Therefore a normal disc has rich autonomic connections and is innervated by multiple spinal segments, an arrangement that explains the diffuse and non-specific nature of the pain originating from the IVDs, akin to the pain from abdominal viscera such as appendix and spleen.

Pathophysiology of Degenerative Disc Disease

Degenerative changes within the disc are commonly seen in asymptomatic individuals, especially with advancing age. However, extensive and often isolated degenerative disc changes are also seen in younger patients with LBP (see Fig. 29.4).[93] Therefore degenerative disc changes may represent both a painless physiologic consequence of aging and also a pathologic and painful



• **Figure 29.7** Schematic representation of normal intervertebral disk components and innervation. *AF*, Annulus fibrosus; *NP*, nucleus pulposus.

phenomenon.[94] A host of factors have been shown to influence early and progressive disc degeneration, including genetic predisposition, diminished blood supply (from causes such as smoking and vascular insufficiency), increased mechanical stress (such as from repeated heavy lifting, contact sports), obesity, and traumatic injury to the cartilaginous end plate.[95–99] These factors can imbalance the tenuous intradiscal milieu, both in the NP and in the AF. In the NP, such imbalances can cause dysfunction (senescence) and decline (apoptosis and necrosis) of the NP cell population, enhanced MMP activity, and increased cytokine or inflammatory mediator content.[100–102] These changes would reduce the NP proteoglycan and water content, diminish its hydrostatic pressure, and would render the NP compressible, exposing the AF to direct axial compression.[86] The axial stress to the AF would eventually lead to its stress failure and loss of collagen, and development of AF fissures that spread outward toward the periphery.[103] These NP and AF structural changes affect the biomechanical properties of the entire disc and cause it to shrink and become less plastic.[104]

Clinical Significance of Degenerative Disc Changes

The reduced disc height and lessened disc pliability can alter the disc and spinal dynamics and can increase the stress loading across the disc itself and the adjacent spinal and paraspinal structures. Consequently, the disc and the contiguous facet joints, muscles, and ligaments, following the local injury and repair responses, can undergo a variable degree of inflammatory changes, increased vascularity and innervation, fibrosis, sclerosis, hypertrophy, new bone formation, and arthritic changes. Several well-recognized painful LBP syndromes can be distinctly linked to degenerative disc changes, including HD, IDD, LFS, LSS, SIJD, MFPS, and Modic changes seen in the adjacent vertebral bodies.[105–107] The symptoms can also arise from the involvement, either from direct pressure or because of the inflammatory changes, of the neural structures housed within the spinal column. Although most of the LBP syndromes have been described individually, they can also be linked directly or indirectly to DDD. However, to further complicate the diagnostic algorithm, the degree of degenerative disc change evident on imaging studies correlates poorly to the symptoms of LBP experienced by patients.[108]

Internal Disc Disruption

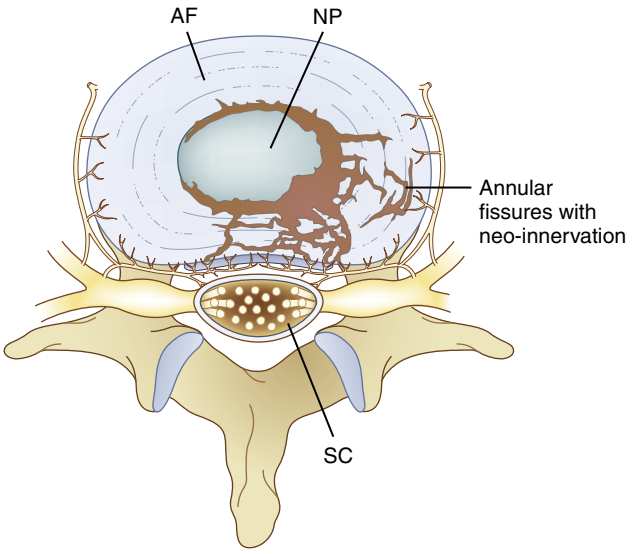
The role played by the disc itself as a source of LBP is poorly understood and, because of minimal innervation of healthy nonpainful discs, has remained controversial.[83] The ambiguity of this source of low back pain is illustrated by the many terms used to describe a painful disc: *IDD*, *discogenic pain*, and *painful DDD,* among others.

Historical Background

Though the concept of IVD as a source of pain was first espoused as early as 1947,[109] the term *IDD* was not used until 1986.[110] The term was coined based on the observation that discs producing pain upon contrast injection during discography, which at that time was the most common diagnostic method for diagnosing an HD, often appear morphologically intact on plain x-rays. Therefore a diagnosis of IDD was rendered almost entirely based on subjective pain responses generated during provocative discography. This exclusively subjective criteria, confounded by a host of psychosocial and somatization influences, led to intense controversy.[111] The validity of provocative discography was seriously challenged, showing a high false-positive rate of 37%.[112] However, these results were widely criticized,[113] and a subsequent study showed a false-positive rate of 0%.[114] As a result of continued scrutiny from the medical community,[111] provocative discography is now assessed using stringent criteria that were adopted to reduce false-positive rates. The International Spine Intervention Society criteria for provocative discography include 1) concordant pain response; 2) presence of at least one disc level with no pain on provocation (the control disc level); and 3) evidence of disc disruption on post-discography CT scan (one or more annular tears extending to the outer AF).[115] To improve the specificity of provocative discography, pressure manometry is often used, and the pressure discography can ostensibly identify painful discs with minimal stimulation.[116]

Pathology of Internal Disc Disruption and Discogenic Pain

Positive pain response on provocative discography has been linked to a host of disc lesions.[117–124] Specimens of discs from patients with concordant pain on discography have been shown to contain vascularized granulation tissue fissures that extend from the NP to the outer AF (Fig. 29.8).[122–124] These granulation tissue zones correlate with the annular fissures seen on post-discography CT scans,[122] and the high-intensity zones seen on MR imaging.[123] In a healthy disc innervation and vascularity are limited to the outer one-third of the AF, but discs with positive pain on provocative discography are highly vascular and richly innervated.[92,118] The nerve fibers found along the AF fissures consist of two distinct varieties:[122] 1) nerve fibers accompanying neovascularization, which are likely vasoregulatory, and 2) free nerve endings, which penetrate deep into the inner AF and NP, are high in substance P, and are likely nociceptors.[118,119] These granulation tissue zones are abundantly infiltrated with mononuclear cells and exhibit strong expression of nerve growth factors, which may contribute to nerve ingrowth and accelerated disc degeneration.[121,124] These discs are also high in inflammatory mediators[120] that can sensitize



• **Figure 29.8** Schematic depiction of lesions of internal disk disruption. *AF*, Annulus fibrosus; *NP*, nucleus pulposus; *SC*, spinal cord.

the neo-nociceptors and maintain a state of hyperalgesia within the affected disc. Thus the pain generated can be aggravated with mechanical stress, such as axial loading, and can be elicited with minimal stimulation on discography, i.e. a chemically sensitized disc instead of a mechanically sensitized disc, which requires higher pressures.[125] Innervation of the disc by nociceptors, presence of inflammatory mediators and inflammatory cells, and the abundance of sympathetic connections at the spinal cord level provide a ready substrate for the origin of discogenic pain. However, it remains uncertain whether IDD is a distinct disease entity or if it denotes early-onset, progressive and painful DDD. Factors discussed above that predispose to early and progressive DDD are also central to the etiology of IDD. However, there is no test currently available that can objectively and reliably detect the pathologic lesions of IDD. Regrettably, the subjective concordant pain response on disc provocation, coupled with morphologic abnormalities seen on post-discography CT scan, currently remains the only means of diagnosing IDD. In addition to the disc lesions described, often causing chronic LBP, acute forms of disc injury causing intense and abrupt LBP have also been described.[126]

Clinical Findings

The exact incidence of IDD in patients with LBP is unknown. However, a preliminary study showed that the incidence of IDD in a group of patients with chronic LBP was as high as 40%.[127] Another study showed that 73% of the patients with severe acute LBP had greater than 70% pain relief after intradiscal injection of local anesthetics.[126] This study indicated that acute disc pathology is responsible for the equally high incidence of severe acute LBP. Both studies claimed that the incidence of disc related pain was greatest in patients younger than 40 years of age, and the pain was located primarily in the low back and buttock regions. The onset of pain was precipitated by a torsion injury of the low back and was exacerbated by axial loading such as with prolonged sitting and standing. Although the pain experienced from disc pathology is characteristically axial in nature, it may also refer to the lower extremities in a non-dermatomal distribution.[128]

Treatments for Discogenic Pain

Treatments for IDD and painful DDD are principally palliative in nature as the available treatments cannot reverse the pathologic changes described above. Among the variety of minimally invasive treatment options available are several disc-heating modalities. Intradiscal electrothermal therapy (IDET) involves heating the posterior AF by a percutaneously placed heating coil.[129] Based on joint arthroscopy, IDET aims to shrink the AF collagen and coagulate the neo-nociceptors. However, its exact mechanism of purported effects is not clear.[130,131] The outcome studies of IDET are mixed, and the reported efficacy ranges from minimal benefit[132] to highly successful.[129] The theoretical basis for surgical treatments for IDD and discogenic pain rests on the complete removal of the painful disc followed by fusion of the adjacent vertebral bodies. However, the results of spinal fusion for discogenic pain using the various techniques discussed previously are also mixed, raising serious doubts about the efficacy of spinal fusion.[133] Loss of spinal mobility from fusion has also been linked to accelerated disc degeneration at the adjacent spinal levels. Artificial disc replacement was introduced to obviate some of the problems associated with spinal fusion surgery. However, outcome studies of disc arthroplasty show results similar to spinal fusion with the added problems of device longevity and high complication rates.[134] Treatments that can restore the disc matrix composition prior to the irreversible damage to the disc and the contiguous structures have been proposed and include biologic treatments such as gene therapy, tissue engineering techniques, and stem cell transplantation.[135,136] However, these therapies remain experimental and are not reimbursable by insurance. The anaerobic disc environment, the immense pressures sustained by the disc, and the ubiquitous presence of the inflammatory mediators likely render the disc environment hostile to this class of interventions. In summary, the currently available treatments for discogenic pain are mainly symptomatic or questionably efficacious. They can also cause substantial complications and cannot restore the disc function or prevent further deterioration, leaving ample room for additional research and new treatment modalities.

Lumbar Facet Syndrome

There is a detailed discussion on the pathogenesis, diagnosis, and treatment of facet syndrome in Chapter 31 of this textbook. In this chapter, we will present a succinct overview to complete the discourse on LBP syndromes.

Anatomy

The lumbar facet or zygapophyseal joints (LFJs) are synovial joints composed of an articular surface, synovial membrane, fibroadipose meniscoid, and fibrous capsule.[137] These paired joints are located dorsally at the junction of the lamina, pedicle, and the base of the transverse process. Each joint is composed of two articular processes, the superior and the inferior, which project from the corresponding vertebrae. The orientation of facet joints is distinct at the lumbar, thoracic, and cervical levels, with the LFJs having a curved and oblique profile. The medial branch (MB) of the posterior primary ramus traverses the base of the superior articular process (SAP) at its junction with the transverse process to innervate both the facet joint at the same level and the vertebral level below. Each facet joint receives innervation from its corresponding vertebral level and the vertebral level above. The course of the MB is relatively fixed as it originates from the dorsal ramus, proximally at the base of the SAP, and passes under the mamillo-accessory ligament. The L5 dorsal ramus passes over the sacral ala at the base of the sacral SAP.[138] The fibrous capsule and the synovium of the LFJs are richly innervated by nociceptive fibers.[139]

Historical Background

LFJs were first proposed as a potential source of pain in the early 1900s,[16] and the term *facet syndrome* was introduced as early as 1933.[140] Several investigators have since reproduced pain in the low back and the proximal leg by injecting hypertonic saline (a physiologic irritant) into the facet joints.[141–143] The relief of pain in patients with chronic LBP by intra-articular facet joint injections of local anesthetic and steroids was first reported by Mooney and Robertson in 1976.[142]

Pathophysiology

Degenerative changes in the facet joints frequently follow DD and accompany degenerative changes in the discs and the neural canals, contributing variably to the patients' overall LBP. However, the exact cause of pain originating from the LFJs is often undetermined, and isolated facet joint pathology is rare. The known

• BOX 29.4 Pathologic Lesions That Can Cause Lumbar Facet Syndrome

Systemic inflammatory arthritides
- Rheumatoid arthritis
- Ankylosing spondylitis

Degenerative arthritic changes
Villonodular synovitis
Synovial cysts
Infections
Microtrauma
- Microfractures
- Capsular and cartilaginous tears

Meniscoid and synovial entrapment
Joint subluxation

causes of independent facet joint pathology include systemic inflammatory arthritides, e.g. rheumatoid arthritis and ankylosing spondylitis, synovitis, and infections (Box 29.4).[144] Microtrauma to the LFJs, including microfractures and capsular and cartilaginous tears, have also been observed in postmortem studies.[145] However, these are undetectable by routine imaging studies, and their role in causing chronic LBP is unknown.[145] Meniscoid and synovial entrapment and joint subluxation are other proposed causes of pain potentially originating from LFS.[146] Notwithstanding, the degenerative arthritic changes, often accepted as the most frequent source of LFS, are observed both in symptomatic and asymptomatic individuals. Moreover, the correlation of degenerative arthritic changes visible on imaging studies and the outcome of diagnostic facet joint injections is poor.[147]

Diagnosis

The typical features of LFS include unilateral or bilateral LBP, frequently referred to as the buttocks, groin, hip, or thighs but infrequently present below the knee joints (Box 29.5).[148] The pain is often exacerbated by arching or twisting movements and with prolonged standing or sitting, and it is reportedly relieved by forward flexion, rest, and walking. Pertinent physical examination findings include painful limitation in low back extension, absence of neurologic deficits, a negative SLR test, and localized paravertebral tenderness over the facet joints. However, many investigators report a lack of consistent clinical findings in patients who respond positively to diagnostic facet joint injections.[149] Even though some have suggested a correlation between the arthritic findings on imaging and the pain relief from diagnostic injections,[150] the imaging findings are generally unable to reliably predict facet joints as a source of pain.[151]

• BOX 29.5 Clinical Features of Lumbar Facet Syndrome

Low back pain
Pain referred to the groin, hip, and posterior aspect of the thigh but rarely below the knees
Pain exacerbated by twisting and extension of the low back region but relieved by forward flexion
Pain with prolonged sitting or standing and relieved by rest and walking
Localized tenderness over the facet joints
Lack of neurologic signs
Normal straight-leg raise test

Diagnostic Injections for Lumbar Facet Syndrome

Despite the various controversies, analgesic response to targeted, low-volume, intra-articular, local anesthetic facet joint injections, or medial branch blocks (MBBs) currently remains the only accepted standard for establishing pain originating from LFJs.[148,149,152] The suspected painful facet joints injected are either those found most tender on the physical examination or, in the absence of any localizing signs, the lowermost joints, i.e. the L5/S1 and L4/5 joints, because these joints are most commonly affected.[149] Fluoroscopic guidance and the use of the coaxial needle insertion technique are often considered essential for intra-articular needle placement.[149] The injectate volume is generally less than 2 mL as larger volumes can cause capsular injury and leakage of contrast material into neural foramina and epidural space, resulting in loss of diagnostic specificity. A small volume of contrast medium (0.2 to 0.3 mL) may also be injected prior to the local anesthetic injection to adequately delineate the joint space. MBBs performed by injecting a small volume (<1 mL) of local anesthetic at the junction of the transverse and the SAP (the "eye of the Scottie dog") have been shown to have equal diagnostic sensitivity.[149] Injection of a small volume of contrast medium prior to the local anesthetic MBBs, has been advocated to confirm the correct needle placement and rule out intravascular needle tip location. MBBs are also useful when the joint entry is challenging, e.g. in patients with severely degenerated joints or after non-fusion spine surgery, and are preferable prior to the MB rhizotomy as they allow direct testing of the nerves targeted for the subsequent neurotomy. Avoidance of systemic analgesics, or the use of only short-acting drugs, and the resumption of pain provoking activities after the diagnostic injection, can facilitate the evaluation of the analgesic response after the diagnostic blocks. Local anesthetics of different duration, used on two separate occasions (double comparative blocks), with the patient reporting corresponding duration of pain relief, can enhance diagnostic specificity.[152] Determined by a single set of diagnostic injections, the prevalence of LFS varied from low of 7.7% to high of 75% in a group of patients with chronic LBP. However, it varied from 15% to 40% when the more stringent double comparative block criteria were used.[152] In addition to the wide variation in the reported prevalence, a placebo response rate of almost 40% was reported when a single set of diagnostic blocks was employed.[153] Therefore double comparative blocks are generally recommended for appropriate diagnosis of LFS to avoid the unacceptably high false-positive response rate of the single diagnostic procedure.

Therapeutic Interventions for Lumbar Facet Syndrome

Lumbar Facet Joint Injections: Based on the practice of intra-articular injection of steroids in knees and shoulders, intra-articular lumbar facet steroid injections were first performed in 1976.[142] Confirmation of LFS by diagnostic blocks, prior to the therapeutic LFJ injections, is rarely practiced.[154] Pain relief from therapeutic LFJ injections is reported mainly in observational studies with success (pain relief of greater than six months) rates varying between 18% to 63%.[152] However, the few prospective controlled trials of LFJ injections have failed to show therapeutic

efficacy.[152,155] Therefore although it is a common intervention, LFJ injections for LBP are inadequately supported, and the typical steroid dosages used (e.g. 20 to 30 mg of methylprednisolone per joint) remain empirical.

Facet Denervation

Denervation of a painful facet joint, referred to as facet rhizotomy, neurotomy, or ablation, is accomplished by lesioning of the MB at the painful vertebral level and one level above. Although chemical neurolysis and cryoablation have been employed, thermal radiofrequency ablation (RFA) of the targeted MB is the most frequently used technique. Because the distal circumferential radius of an RF lesion is markedly shorter than the median radius, RFA is typically performed by placing an electrode parallel to the path of the target MB, i.e. along the base of the SAP.[156] Optimal electrode positioning is confirmed both radiologically and by appropriate sensory and motor testing (discussed in Chapter 31) prior to the lesion creation. The size of RF electrodes used varies between 18 and 22 gauge, the temperatures range between 80°C and 90°C, and the duration of RF lesioning can last from 60 to 90 s. Larger probe size, longer duration, and higher temperatures can produce larger lesions with a greater likelihood of thermally coagulating the target MB. Routine use of 18 gauge electrodes with a 1 cm exposed tip, lesioning duration of 120 s, and temperature of 80°C have been recommended by some authors.[157] In addition to the several observational studies reporting the efficacy of RFA for LFS, three RCTs of its efficacy are available; while two demonstrated improved chronic LBP following the procedure, the third showed no benefit.[157]

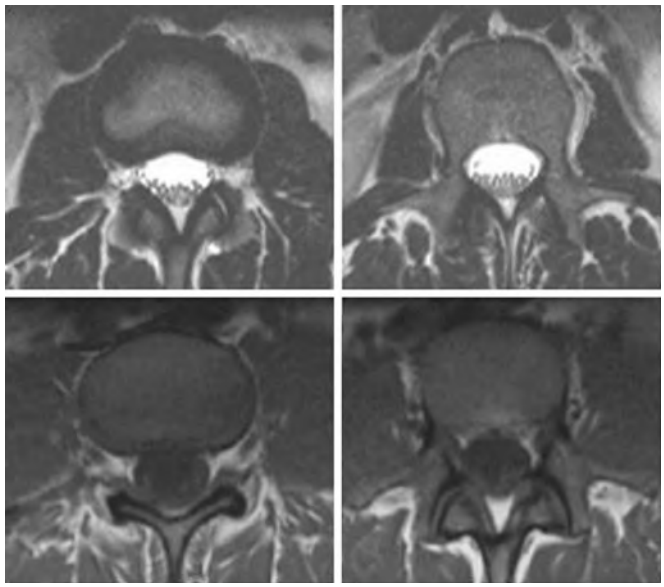
Diagnostic Studies for Low Back Pain

The diagnostic studies employed to ascertain the etiology of LBP can be broadly grouped into imaging modalities, discography, diagnostic blocks, electrodiagnostic studies, and laboratory studies. These studies are detailed in other sections of this book, and only the most pertinent information pertaining to the imaging, electrodiagnostic, and laboratory tests are relayed below.

Imaging Studies

- *Magnetic resonance imaging*: MRI is considered the gold standard in determining the etiology of low back and radicular pain (Figs. 29.9 and 29.10). MRI offers the best resolution of pathologic lesions in the spinal canal, spinal cord, neural foraminae, NRs, and disc spaces and allows evaluation of the entire spine.[69] In patients with a history of previous spine surgery, a contrast-enhanced MRI is recommended to differentiate between scar tissue and possible recurrent disc herniation. Limitations of the MRI include lengthy examination time, claustrophobia, and its effects on metallic bodies. MRI is contraindicated in patients with pacemakers, certain aneurysm clips, or other metallic objects in the body. MRI is the most common imaging modality used to diagnose an HD and LSS as the findings are characteristic and easy to visualize but are also frequently present in older[62] and/or asymptomatic individuals.[158,159] Therefore it is critical that the radiologic abnormalities identified are correlated with the patient's clinical evaluation. The degenerative disc changes seen on the MRI can include disc desiccation (loss of T-2 disc signal intensity), disc bulging, and loss of disc height. As stated, these MR findings are also common in asymptomatic individuals and are of limited value in the diagnosis of painful DDD and IDD.[93,108] Loss of T-2 signal intensity, indicating loss of NP water content (see Fig. 29.4), often referred to as "black disk disease," may be the only indication of early IDD.[160] A high-intensity zone in the posterior AF on the MRI (see Fig. 29.4) has been shown to indicate the presence of a tear in the posterior disc annulus and is closely correlated with positive pain on provocative discography.[123] Nevertheless, the overall correlation of results between discography and the MR features for the diagnosis of IDD has ranged between 55%[161] to almost 100%.[162]
- *Computed tomography*: Although MRI is considered the gold standard spinal imaging modality, CT scan of the spine can be

• **Figure 29.9** Normal T2- and T1-weighted midline sagittal magnetic resonance images of the lumbar spine.



• **Figure 29.10** Normal T2- and T1-weighted axial transdiscal and interdiscal magnetic resonance images of the lumbar spine.

• **Figure 29.11** Normal anteroposterior and lateral plain X-ray images of the lumbar spine.

a valuable and even preferable tool for the evaluation of bony spinal details, e.g. diagnosis of spinal fractures, bony tumors, and abnormalities of the facet joints and lateral recesses. However, in the evaluation of the spinal canal, CT is unable to distinguish between certain lesions (e.g. between an HD or neoplasm), and its routine use for this purpose is discouraged.[163] CT combined with myelography has a resolution comparable to that of MRI. Therefore CT-myelogram can reliably diagnose spinal canal lesions when MRI is contraindicated.[163]

- *Plain radiography*: Plain x-rays of the spine are the most cost-effective and readily available of the imaging techniques. Typical views performed include the anteroposterior, lateral, and oblique spinal images. Plain X-rays of the spine can reveal various bony abnormalities. However, the soft tissue details are difficult to discern (Fig. 29.11). Though spinal fractures and deformities are readily appreciated, the plain X-ray findings of lumbar lordosis, transitional vertebrae, and disc space narrowing are common in asymptomatic individuals.[164] As compared to other modalities, plain radiographs do not permit sectional imaging, and thus sagittal and axial views are not possible. Therefore the "routine" ordering of spinal roentgenograms for LBP is not recommended.[165] Flexion and extension spinal films are often performed, typically after spinal fusion surgery, to evaluate segmental instability as a source of pain. However, the correlation between abnormal vertebral motion and pain symptoms is poor.[166]
- *Myelography*: Though a common test in the past, myelography without spinal CT is an infrequently performed test. It is utilized to detect spinal canal lesions when other studies yield conflicting information, are not available, or are contraindicated.
- *Bone scan*: Increased uptake of the radioactive isotopes by metabolically active inflammatory or neoplastic tissues (disc, bone, ligaments) can help identify lesions such as discitis, osteomyelitis, arthritic conditions, and stress fractures, which are otherwise difficult to ascertain on routine imaging.

Electrodiagnostic Studies

Electrodiagnostic studies, including electromyography (EMG) and nerve conduction velocities (NCV), are useful in establishing the radicular nature of symptoms when the clinical features are inconclusive or are indistinguishable from other syndromes such as peripheral neuropathy. In contrast to the imaging studies, the combined results of EMG and NCV have higher specificity for the diagnosis of LRS.[167] However, EMG and NCV cannot determine the etiology of LRS, the results correlate poorly to the anatomic level of the radicular lesions ascertained, and their routine use is not recommended.[36] Somatosensory evoked potentials (SSEPs) can pinpoint the site of nerve dysfunction, and their use is generally limited to ascertaining the location of intraoperative nerve injury.

Laboratory Tests

The various hematologic and serologic tests such as complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, antinuclear antibodies, HLA-B27 antigen, and urinalysis are useful when spinal infections and inflammatory and rheumatologic disorders are suspected.

Symptomatic Treatments for Low Back Pain

Various remedies that aim to provide symptomatic relief of pain and improve function, despite the etiology, are used extensively to manage LBP. These strategies are briefly discussed below:

- *Medications*: Multiple categories of medications employed for the management of LBP, often in variable combinations, include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, opioids, oral steroids, muscle relaxants, membrane stabilizers (e.g. gabapentinoids), and neurotransmitter reuptake inhibitors (e.g. serotonin-norepinephrine reuptake inhibitors, tricyclic anti-depressants). NSAIDs are by far the most commonly used drugs and have been shown to have efficacy in the management of acute radicular symptoms.[168] Acetaminophen and NSAIDs are particularly helpful in providing symptomatic relief of acute flares of LBP. Opioids are widely prescribed for various LBP conditions. However, because of the significant potential for abuse and the chronic nature of the LBP syndromes, the use of opioids should be limited to short courses and only for acute exacerbations of LBP.[169] Systemic corticosteroids are prescribed, both orally and parenterally, for the various LBP syndromes, particularly for an acute disc herniation. However, evidence supporting this practice is lacking.[170,171] Calcitonin has been found to be beneficial for LSS resulting from Paget's disease.[172]
- *Physical therapy*: Physical therapy modalities, both active and passive exercises, are routinely advocated to improve function and reduce pain. Active exercises, deemed more effective, can boost muscle strength and conditioning, while passive maneuvers aim to increase range of motion, increase flexibility, and reduce stiffness.[173] Regularly performed active exercises can also promote weight loss, promote cardiovascular fitness, and improve tolerance of other exercise programs. Flexion-based exercises, e.g. stationary bicycle and inclined treadmill, may be helpful in LSS by increasing the cross-sectional area of the spinal canal and improving microcirculation of the neural elements.[174] Aquatic therapies, particularly those that stretch hip flexors and hamstrings and strengthen the core abdominal and trunk muscles, may also be useful in LSS.[174] The overall role of physical therapy for the treatment of various LBP syndromes remains uncertain.[40]

- *Psychological treatments*: Behavioral therapy, especially cognitive behavioral therapy and biofeedback, have been shown to have modest efficacy in patients with chronic LBP.[175]
- *Activity Modification*: To promote natural healing and recovery, avoidance of aggravating activities, and relative rest, is recommended during acute flare-ups of the various LBP syndromes. However, the potential for deconditioning and stiffness limits recommendations of prolonged inactivity.[169] Instead, a continuation of activities within the limits imposed by the pain is recommended as it results in faster recovery.[176]
- *Bed rest*: Though a common treatment in the past, prolonged and strict bed rest is no longer advocated for the management of LBP conditions because of its multiple potential harmful effects.[176,177]
- *Bracing*: Lumbar bracing, including rigid, semi-rigid, and soft braces and binders, are other methods of immobilizing a painful spine; lumbar binders propose to reduce loads across the lumbar spine. These devices may reduce pain by limiting motion and can provide symptomatic relief. However, the potential for deconditioning and stiffness, along with insufficient evidence supporting their use, limits their recommendation.[178] Overall, to avoid deconditioning and stiffness, the use of braces and binders, particularly the rigid braces, should be limited only to short periods.
- *Traction*: Once a mainstay treatment for LBP, particularly for HD, traction, both in its continuous or intermittent forms, remains unproven and is no longer a popular therapy.[179] Vertebral axial decompression (VAX-D®), a proprietary modality based on traction principles, remains untested.
- *Acupuncture*: Although some studies have shown the effectiveness of acupuncture for chronic LBP, it lacks clear scientific support from rigorous trials.[180]
- *Miscellaneous Treatments*: Chiropractic manipulations, massage therapy, magnets, transcutaneous electrical nerve stimulation, and ultrasound application, often employed for the management of low back and radicular pain, remain unsubstantiated.

Diagnostic Challenges in Patients With Low Back Pain

With their shared etiology, predisposed to by DD, most low back and radicular pain syndromes, including the DDD, HD, LSS, IDD, LFS, SIJD, and even the ubiquitous sprains and strains, can be present concurrently. Despite their distinct pathologic lesions, as discussed earlier in this chapter, these LBP syndromes likely have analogous overall patterns of cyclical injury and repair.[181] The injury sustained by the various spinal and paraspinal structures secondary to DD invokes local tissue inflammatory reactions. These reactions herald the subsequent repair cycles characterized by granulation, endothelial, neural, and fibrotic tissue infiltration. These injury and repair cycles likely correspond to the remissions and relapses characteristic of chronic LBP and plausibly also explain the poor correlation of symptom severity and imaging findings. The presence of many concomitant LBP syndromes and the variability in the pain caused can result in multiple concurrent, asymmetrically present, and vacillating pain generators, which are inconsistently linked to the morphologic changes observed. Hence, the precise recognition of these diverse pain generators in a patient with LBP is challenging. The limitations of the most frequently employed test for LBP (the spinal MRI) were alluded to earlier in this chapter, i.e. the abnormalities can be elucidated in both symptomatic and asymptomatic individuals.[158,159] Other frequently employed tests such as the diagnostic local anesthetic blocks and provocative and/or local anesthetic discography are also compromised by their subjective nature and the fact that the placebo effect can result in low specificity and high false-positive rates. Hence, the accuracy with which pertinent pain generators can be elucidated in patients with LBP rests on the keen awareness of their concomitant presence and vacillating nature. The spinal imaging modalities in this context can define the extent of the disc and the contiguous spinal and paraspinal structural involvement from DD. Armed with this background, a meticulous clinical evaluation could delineate the plausible pain generators. Pertinent diagnostic blocks and provocative tests, corroborating the clinical and the radiologic findings, can further enhance the diagnostic accuracy and pinpoint targets for surgical and minimally invasive interventions. However, although ordering tests selectively and correlating their results with clinical findings should prevent inappropriate diagnoses and improve outcomes,[35] the precise source of LBP can remain elusive.

Approach to Managing Patients With Low Back Pain

The extensive list of conditions causing LBP, alongside the diagnostic impediments discussed, necessitate a clear approach to managing patients with LBP. Indiscriminate diagnostic workup is not only costly but would also engender results that may be unrelated and misleading. Therefore in 1994, the Agency for Health Care Policy and Research (AHCPR) developed guidelines to identify and treat, at first, only the conditions deemed life threatening and/or that can cause neurologic compromise. Conferring the AHCPR guidelines, these "specific" conditions (i.e. malignancies, inflammatory conditions, traumatic injuries, and CES), defined at the outset of this chapter, can be recognized by systematic clinical evaluation of these patients.[35] The signs and symptoms indicative of the "specific" LBP conditions, referred to as "red flags" (Table 29.2) cited in the AHCPR publication, include:[35]

- *Extremes of age*: Patients younger than 20 years old often present because of congenital and developmental anomalies, while those over 50 are at higher risk of developing neoplasms, pathologic fractures, infections, and life threatening extra-spinal processes as a cause of their LBP.
- *Duration of symptoms*: Compared to chronic LBP (pain greater than three months), symptoms of less than three months duration, acute and subacute LBP, can indicate a more sinister etiology.
- *History of trauma*: History of significant trauma, or a less serious injury in older patients and those with serious medical conditions, may result in simple or pathologic fractures that may require further workup.
- *Constitutional symptoms*: Fever, chills, malaise, night sweats, and unexplained weight loss suggest a serious underlying disorder such as malignancy or infection.
- *Systemic illness*: History of cancer, recent bacterial infections (e.g. serious respiratory or urinary tract infections), intravenous drug abuse, immunosuppression (e.g. infection with human immunodeficiency virus, organ transplantation, and chronic corticosteroid use) could increase the likelihood of pathologic fractures, epidural and vertebral body abscesses, and metastasis.
- *Unrelenting pain*: Pain of benign etiology is typically relieved with rest and supine position, especially at night, while pain from serious pathologic conditions can be unrelenting, worse at night, and unresponsive to rest and analgesics.
- *Cauda equina syndrome*: The signs and symptoms of CES are discussed earlier in the chapter (Box 29.2).

TABLE 29.2 "Red Flags" in the Clinical History of Patients With Low Back and Radicular Pain

Red Flag	Implications
Red Flags in the History	
Age younger than 20 years	Congenital and developmental disorders, spondylolisthesis
Age older than 50 years	Malignancy, pathologic fractures, infections, AAA
Short term symptoms of < three months	More serious etiology
Trauma	Fractures
Fever, chills, malaise, night sweats, weight loss	Malignancy, osteomyelitis, abscess, fracture
History of cancer, HIV, chronic steroid use, IV drug abuse, immunosuppression	Malignancy, osteomyelitis, abscess, fracture
Unrelenting pain	Malignancy, osteomyelitis, abscess, fracture
Incontinence, saddle anesthesia, bilateral neurologic symptoms	Cauda equina compression
Red Flags in the Physical Examination	
Fever	Malignancy, osteomyelitis, abscess
Motor weakness, diminished reflexes, saddle anesthesia, weak anal sphincter	Cauda equina compression
Spinous process tenderness	Fracture

AAA, Abdominal aortic aneurysm; *HIV*, human immunodeficiency virus; *IV*, intravenous.

Contemporary algorithms for managing LBP,[5] consistent with the AHCPR recommendations, recommend first excluding specific disorders by identifying "red flags" in the patient's history and physical examination. In their presence, to rule out these specific conditions, the patients are offered further diagnostic workup and possible intervention, while their absence translates to a diagnosis of non-specific LBP (NsLBP). Though by definition, NsLBP denotes an unknown etiology, the pain in these patients is customarily assumed to be from "degenerative" conditions with favorable natural history. Self-limiting and expected to resolve spontaneously, NsLBP is managed expectantly; i.e. the patients are not afforded diagnostic tests or specific treatments but rather preventative strategies and generic therapies for the symptomatic relief of pain and disability.[5,35,36] In the absence of a suitable recovery during the period of expectant management, which typically occurs over a period of six to eight weeks, NsLBP patients may be offered further diagnostic workup and interventions. Such intercepts are subjective and adopted variably across different clinical practices.

Limitations of the Current Approach

The "specific" disorders are uncommon (< 5%), and over 95% of the patients with LBP will ostensibly have "non-specific" causes. Hence, following the current methodology, a vast majority of the patients presenting with LBP will undergo no diagnostic workup, receive no specific treatment, be provided no clear explanation for their symptoms, and be given no express recommendations for the prevention or further deterioration of their condition. Even in instances in which diagnostic workup and specific treatments were to be provided, in the absence of the expected recovery, these decisions can be uncertain, deferred, or eschewed altogether. Consequently, many patients seek alternate care methodologies and are lost to follow up. The designation of LBP to "specific" and "non-specific" groups, based only on the clinical criteria, can also be subjective and interpreted variably by the diverse providers involved.[182] Remarkably, when the "specific" disorders are excluded, the LBP caused can be from a range of well-defined conditions we examined earlier in this chapter and are discussed elsewhere in this book. Notwithstanding the distinct pathophysiology and natural history, many of these "non-specific" conditions have existing treatments and explicit preventative strategies, and others, with their greater understanding over the recent years, may have looming treatment options. Additionally, though considered self-limiting, these "non-specific" conditions can be progressive and irreversible and may cause significant long-term pain and disability. Paradoxically, the "specific" disorders are not invariably progressive, nor will they necessarily lead to neurologic injury and/or demise, e.g. certain compression and non-displaced spinal fractures, stable deformities, chronic inflammatory, and metabolic conditions, and even some neoplasms, necessitate only careful monitoring and supportive care. Hence, cataloging LBP to "specific" and "non-specific" groups might rest on arbitrary criteria, which can leave a vast majority of patients with LBP with unclear management strategy or understanding of their symptoms. Such lack of guidance could also result in incapacitating pain and disability from the irreversible progression of these conditions. Therefore an alternative strategy based on a clear understanding of these conditions, which would improve patient satisfaction, optimize care and prevention, and will have superior outcomes, is desirable. One such, ostensibly conflicting approach is to attempt to determine the cause and offer specific therapies and preventative strategies to all the patients with LBP. With superior knowledge of the causative conditions, meticulous clinical evaluation, and the targeted use of the diagnostic tests, the costs of indiscriminate and "routine" diagnostic testing could be curtailed. For instance, patients suspected of omnipresent sprains, strains, and MFPS would undergo no diagnostic testing, as no testing is available to confirm these conditions. Following this strategy, the patients could be informed of the possible nature of their LBP, lessening their discontent, and specific therapies and preventative strategies can be initiated early in the course of these otherwise progressive conditions. By way of example, early recognition of DD is vital, even though specific treatments that can arrest or reverse early DD are currently not available because specific preventative strategies (e.g. explicit work related lifestyle modifications) could be introduced early to slow the progression of DD to subsequent advanced LBP syndromes.

Treatment Challenges, Prevention, and Future Directions

The diagnostic impediments mentioned above are confounded by substantial treatment challenges in patients with LBP. The available treatments, discussed under the various chapter subheadings, can be summarized as a range of surgical, minimally invasive, conservative, traditional, and alternative therapies.

These therapies are offered by diverse providers with varied backgrounds who tend to prefer their own methodologies or field of treatment. Consequently, analogous conditions are often treated by profoundly different approaches, which can lead to an immense variability in the care provided.[182] Furthermore, the available treatments aim mainly to provide symptomatic relief, improve strength and flexibility, reduce inflammation, and in the surgical interventions, in particular, provide neural decompression and spinal stability. Crucially, therapies aimed to resolve early DD and restore disc matrix composition prior to the irreversible damage to the disc and the contiguous structures are not well-developed. Consequently, the symptomatic relief afforded by many treatment modalities is typically either incomplete or short-lived as it does not address the underlying DD. In particular, low back surgery can cause worsening LBP, which is proportionate to the extent and the number of low back surgeries performed.[183] As "regenerative" therapies are nascent and traditional treatments lack efficacy, early initiation of specific preventative strategies to curb DD and stop the progression of disc and contiguous structural injury is vital. Premature DD can originate from a myriad of genetic and environmental influences. Polymorphism at various connective tissue gene loci can render the IVD vulnerable to injury and specific occupational and lifestyle external influences predisposing to DD, as discussed earlier in the chapter. Hence, individuals with specific phenotypes who are exposed to precipitating environmental influences are especially prone to early DD and must be identified. Furthermore, recognition of early DD prior to significant disc injury and any symptoms is feasible, as MRI can discern early loss of NP proteoglycan and water content.[184] Screening high-risk individuals could reveal early DD and premature disc damage so that early preventative actions can be taken. Although fiscal impact renders screening MRI impractical at the present time, similar preventative measures can be adopted in patients with new onset LBP to curb the progression of DD, which may lessen the overall burden of LBP on the individual patient and greater society.

Key Points

- LBP often emanates from spinal and paraspinal structures, but it may also refer to adjacent joints or even viscera.
- LBP in any particular patient is often caused by multiple, variable, asymmetric, and vacillating pain generators.
- Causative conditions of LBP are managed by cataloging those that are potentially life threatening and/or can cause neurologic compromise and those that are presumed to be self-limiting.
- Despite carrying low mortality burden, the self-limiting conditions that cause LBP can be progressive, irreversible, and may result in long-term pain and disability.
- Many distinct low back syndromes notably have a shared primary origin that derives from dysfunction of the IVDs.
- The general pattern of most painful primary etiologic processes is similar in that tissue injury is followed by inflammatory changes and fibrotic repair.
- Injury and repair cycles that result in chronic LBP often originate in an initial injury to the disc and then progress to painful episodes with remissions and relapses consistent with the pattern of tissue injury and repair.
- The tests available for the diagnosis of these LBP syndromes, particularly the array of imaging studies, give only a snapshot of the evolving pathologic processes and generally are unable to clearly pinpoint the primary pain generators.
- Expertise in the conditions causing LBP, meticulous clinical examination, and confirmation of the disease state with available diagnostic tests are all necessary to appropriately assess patients with LBP.
- The treatments available for the management of various low back conditions, even those publicized as regenerative, cannot reverse or even arrest the underlying causative pathologies.
- Currently available treatments generally provide symptomatic relief with variable efficacy, but because of an absence of effect on etiologic processes, the relief provided is typically partial and/or temporary.
- Surgical treatments often provide inadequate pain relief and, in addition to their invasive nature and high complication rate, may also result in worsened LBP.
- Pertinent indication for spine surgery, especially in the context of non-specific LBP, is progressive neurologic compromise and not LBP.
- As treatments cannot mitigate the pathologic processes causing the various LBP syndromes, a clear understanding of their prevention by measures adopted early in vulnerable patient populations and in afflicted patients to minimize progression remains paramount.

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30

Buttock and Sciatica Pain

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Buttock pain can originate from a heterogeneous collection of pathologic conditions. Similar to low back pain, the precise diagnosis and treatment of pain in this region can be challenging. This chapter focuses on pain largely experienced in the buttock region *and* originates below the lumbosacral junction. Pain generators can be intrinsic to the buttock region, such as the sacroiliac joint complex (SIJC), coccyx, piriformis muscle and sciatic nerve (SN), ischiogluteal bursa, and other muscles in the hip girdle and pelvic region, as well as referred from other regions such as the viscera of the abdomen or pelvis. Pain experienced in this region can also be caused by disorders originating in the lower back, such as radiculopathy and facetogenic pain, which are discussed in other chapters of this textbook. Less common but nonetheless important causes of buttock pain, such as fracture, infection, and neoplasm, are also beyond the scope of this chapter.

Sacroiliac Joint Complex (SIJC) Pain

Epidemiology

Pain generated by the SIJC is an underappreciated source of the presenting complaint of low back pain (LBP), with a reported prevalence rate ranging between 10% and 33% in individuals with a suspected mechanical etiology predominantly below L5.[1,2] However, the diagnosis of SIJC pain depends on the diagnostic criteria, with more stringent criteria resulting in lower prevalence rates based on the response to injections. In a review by Kennedy et al. using ≥50% pain relief based on single blocks yielded prevalence rates between 60% and 65% in three studies. Based on the more stringent criteria of ≥75% pain relief with double-blocks, prevalence rates ranged from a low of 10% to a high of 33% based on five studies.[2]

Etiology

The sacroiliac joint is a diarthrodial synovial joint, and pain in this region may arise from numerous bony and soft tissue structures, including the fibrous joint capsule, the sacral and iliac bones (sacral degeneration generally occurs after degenerative changes in the ilium), adjacent muscles (e.g. latissimus dorsi, gluteus maximus and medius, erector spinae, iliacus, rectus femoris), and ligaments located both anterior and posterior to the articulation. Soft tissue, periosteum, and the joint capsule all contain nociceptors. Therefore all potential sources of pain. Although the ligamentous connections in the SIJC contain the greatest surface area and are most likely to be injured with trauma, the density of nociceptors is greatest in the joint capsule.[3] Because of the myriad potential pain generators within and surrounding the sacroiliac joint (SIJ) region, the SIJC may be more appropriate.

SIJC pain may result from repetitive stress or traumatic inciting events. Several studies that examined the causes of injection-diagnosed SIJC pain found that a specific inciting event was reported in 40% to 50% of cases, with the most common antecedents being motor vehicle collisions, falls, cumulative stressors, and pregnancy.[4–6] Pregnancy is associated with SIJC pain because of anterior weight gain, change in posture, hormone-induced relaxation of the ligaments in the last trimester, and trauma to the pelvis associated with childbirth. A prospective study performed in 355 parturients found a LBP prevalence rate of 49%, while another study conducted in 1500 pregnant women with new-onset LBP reported that 79% stemmed from SIJ dysfunction based on functional testing.[7,8] Of note, the reported prevalence in parturients may be overestimated, as dual diagnostic blocks cannot be performed during pregnancy. Leg length inequality has also been implicated as a potential etiology of SIJC pain, as leg length inequality has been shown to asymmetrically distributes loads across the SI joints. Forces are increased on the side of the longer leg and increase with greater leg length inequality.[9] An additional source of SIJC pain is prior surgery. Surgically induced SIJC pain may be difficult to distinguish from lower lumbar pathology, although timing and pain referral patterns may provide clues. Clinical studies evaluating prevalence rates based on response to diagnostic injections after spinal fusion have reported rates between 32% and 43%, being more common after fusion to the sacrum.[10] SIJC pain after fusion can result from accelerated joint degeneration, ligamentous disruption, or simply increased mechanical stress because of load transfer to adjacent segments below the fusion (particularly with a fusion to the sacrum).

Extra-articular vs. Intra-articular Pathology

SIJC pain may be classified as extra- or intra-articular (bone, fibrous capsule, articular cartilage, synovium) and can have different causes (Table 30.1). In studies that have evaluated the response to SIJ injections, one large retrospective study found combination intra- and extra-articular injections to be superior to intra-articular blocks,[11] one found extra-articular injections to be better for immediate pain relief,[12] while a small study designed to evaluate the accuracy of ultrasound injection study reported no difference in short-(24 h) or intermediate- (four weeks) term outcomes.[13] A more recent multi-center, double-blind, randomized trial comparing fluoroscopically guided to landmark-based SIJ blocks[14]

TABLE 30.1 Causes of intra- and Extra-articular SIJ Pain

Intra-articular	Extra-articular
Arthritis (e.g. osteoarthritis, rheumatoid)	Trauma/fractures
Spondyloarthropathy	Ligamentous injury
Trauma	Myofascial pain
Infection	Enthesopathy
Cystic disease	Pregnancy
	Cystic disease

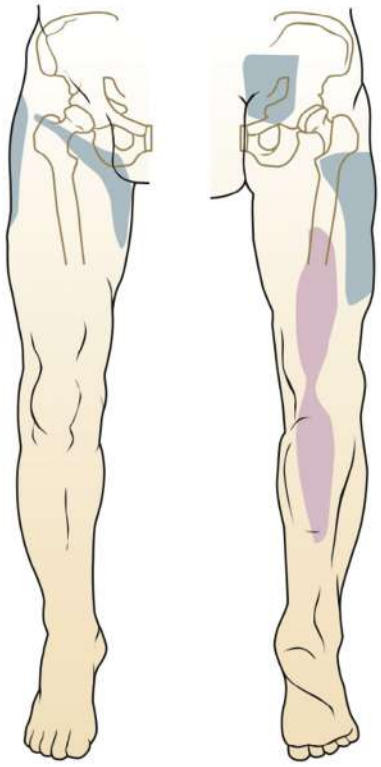
found no differences in immediate pain relief (reflecting prevalence) or one month outcomes between intra-articular and extra-articular local anesthetic and steroid injections. However, those who received intra-articular blocks fared better on some outcome measures at three months. Individuals with intra-articular SIJ pain are more likely to be older and present with insidious onset, bilateral symptoms, and evidence of joint degeneration on imaging. In contrast, those with extra-articular SIJ pain are more likely to be younger, have unilateral pain, report a specific inciting event, and have more prominent tenderness.

Nociceptive fibers and receptors containing calcitonin gene-related peptide and substance P immunoreactive free nerve endings have been noted in the interosseous and anterior ligaments of the SI joint by Szadek and colleagues.[15] Given their findings, the authors recommended extra- as well as intra-articular approaches to diagnostic SI joint injections.

Presentation

The SIJ is the largest axial joint in the body, and consequently, presentation depends on the part of the joint that is injured (i.e. upper vs. lower joint, dorsal vs. ventral joint, ligaments vs. articular surface vs. joint capsule). Multiple studies have shown that SIJC pain is most likely to be concentrated below the L5 spinal level near the posterior superior iliac spine, with upper joint pathology causing pain in the upper buttock region and lower joint pathology causing pain in the lower buttock.[16,17] In a retrospective study, 94% of individuals experienced buttock pain, and 72% had pain in the lower lumbar region.[18] Half of the patients reported pain extending into the lower extremity, with 28% experiencing pain extending below the knee. Fourteen percent had radiation into the groin. Buttock pain extending into the posterolateral thigh is one of the most common presentations (Fig. 30.1). A study by Cohen et al.[5] found that 35% of patients who underwent sacral lateral branch nerve (SLBN) radiofrequency ablation (RFA) experienced pain in their thigh(s). A two part study that sought to determine SIJC referral patterns in asymptomatic volunteers and patients with LBP found the most common presentation to be unilateral buttock pain extending to the posterior and sometimes lateral thigh,[19] while others have found the presence of groin pain to most accurately distinguish SIJC pain from other mechanical sources of LBP. It should be noted that groin pain is a more common presenting symptom in intra-articular hip pathology than in SIJ pain or trochanteric bursitis, although the three conditions are often concurrent.[6,16,20]

Whereas most studies examining SIJC pain referral patterns have been based on maps drawn from patients who respond to intra-articular injections or from pain patterns induced by capsular distension, some investigators have also examined pain patterns based on soft tissue SIJC injections, for example, local



• **Figure 30.1** Pattern of pain from sacroiliac joint syndrome. (From Benzon HT. Pain originating from the buttock: sacroiliac joint dysfunction and piriformis syndrome. In: Benzon HT, Raja S, Molloy RE, et al. (eds). *Essentials of Pain Medicine and Regional Anesthesia*. New York: Elsevier Churchill Livingstone; 2005:356–365.)

anesthetic injection into the dorsal ligaments. In a study of 50 patients who achieved at least 70% pain relief from extra-articular injections, the authors found that the upper ligamentous part of the SIJC generated pain near the posterior superior iliac spine with radiation to the groin, while pain emanating from the middle and lower portions of the SIJC was most prominent in the mid- and lower buttock regions,[16] induced pain from all sections often spread into the posterolateral thigh, but infrequently below the knee. SIJC pain may also occur concurrently with other sources of LBP, with one study finding that 75% of individuals with axial LBP, herniated disc, or lumbar stenosis had radiologic evidence of SIJ arthritis.[21]

Multiple studies have sought to evaluate the predictive value of physical examination findings in establishing the SIJ(s) as the primary pain generator using response to low-volume diagnostic blocks as the reference standard. These studies have generally found that single provocative maneuvers, alignment tests, and mobility assessments possess low sensitivity and specificity for identifying a painful SIJ. However, a systematic review that included 18 studies found that a combination of three provocative tests has sufficient discriminative power.[22,23] The maneuvers provide value in confirming the diagnosis when the symptoms suggest SI joint complex dysfunction and other causes of pain have been eliminated.

Physical examination of the patient with SIJC pain usually revealed tenderness over the posterior aspect of the joint and sacral sulcus. There were no neurologic symptoms such as numbness or weakness. There are several provocative maneuvers designed to stress the SIJC and elicit concordant pain, including the FABER (flexion, abduction, and external rotation), Patrick's test,

Gaenslen's test, Yeoman's (extension) test,[24,25] sacroiliac or posterior shear test, Gillet's test,[25,26] thigh thrust test, pelvic distraction test, and pelvic compression test. Fortin's finger test is also helpful in diagnosis, but it should probably be described as part of the history. Given the complexity of the lumbar, sacral, and pelvic anatomy, SIJC provocative maneuvers often stress structures that are in close spatial and mechanical proximity to the SIJ. This adds complexity to interpreting positive results and necessitates three positive provocative maneuvers to reasonably assure SIJC involvement in a patient's pain.

FABER-Patrick's test (Left SIJC exam) (Fig. 30.2)

- Position: Supine.
- Maneuver: The left leg near the ankle is placed in front of the right thigh above the knee.
- The physician placed one hand over the right iliac crest while the other hand pushed over the medial aspect of the left knee.
- Positive test: Pain over the left SIJ region (also back, buttock, groin)
- Comment: Test stresses the SIJC *and* hip joint, as well as the posterior elements of the lower lumbar spine. Pain because of intra-articular hip pathology, a more common cause of groin pain, is experienced on the side with a flexed hip/knee. Pain originating in the lower lumbar spine, a more common cause of LBP, can be experienced in either laterality.

Gaenslen's Test (Left SIJC exam) (Fig. 30.3)

- Position: Supine. Left leg and lower thigh hanging off the examination table.

• **Figure 30.2** FABER-Patrick's test, left side.

• **Figure 30.3** Gaenslen's test, left side.

- Maneuver: The examiner flexed the right hip and right knee (i.e. the hip joint was maximally flexed). The examiner presses downward over the left thigh (the hip joint is hyperextended).
- Positive test: Pain in the left SIJ.
- Comments: The test stresses both SIJs simultaneously by counter-rotation at the extreme range of motion of the joint. The test also stresses the hip joint and stretches the femoral nerve (the examiner should ensure the absence of hip pathology or conditions affecting the femoral nerve to diagnose SIJ syndrome).

Yeoman's Test (also called Extension Test) (Fig. 30.4)

- Position: Prone.
- Maneuver: The examiner placed one hand above the anterior aspect of the knee and elevated it slightly; the other hand pressed downward over the crest of the ilium.
- Positive test: Pain over the posterior SIJ region.
- Comments: The hip is extended, and the ipsilateral ilium is rotated. The test stresses the SIJ and extends the lumbar spine, and stresses the femoral nerve. It is more specific and reliable than other tests.

Gillet's Test (Fig. 30.5)

- Position: Standing.
- Maneuver: One of the examiner's thumbs was placed on the second sacral spinous process, and the other thumb was placed on the posterior superior iliac spine (PSIS).
- Normal SIJ: The PSIS moves inferior to the S2 spinous process when the patient maximally flexes the hip.
- Dysfunctional or fixed SIJ: PSIS remains at the level of the S2 spinous process or moves superior to the sacrum.

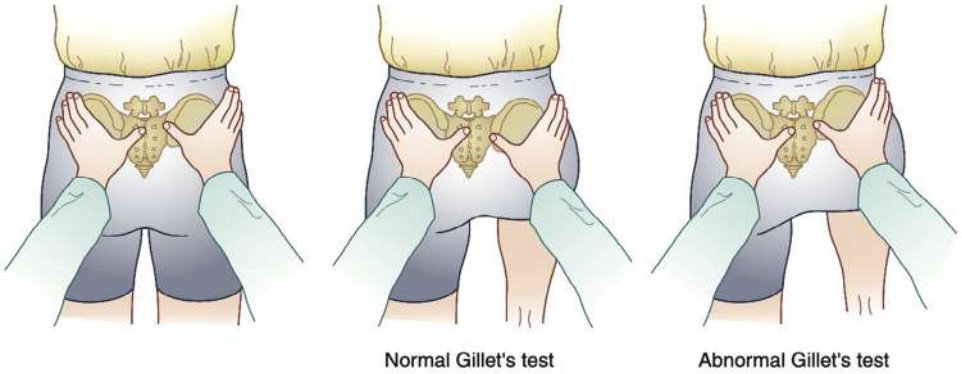
Sacroiliac Shear Test (Fig. 30.6)

- Position: Prone.
- Maneuver: The palm of the examiner's hand was placed over the posterior iliac wing. The shear thrust is directed inferiorly, producing a shearing force across the SIJ.
- Positive test: Pain in the location of the SIJC.

Thigh Thrust Test (Fig. 30.7)

- Position: Prone.
- Maneuver: The patient's hip was flexed to 90°, and the knee was flexed to 90°. The practitioner positions the patient's knee under his or her axilla and applies direct downward pressure through the femur.
- Positive test: Pain over the ipsilateral SIJ region (also back, buttock, groin).

• **Figure 30.4** Yeoman's test, left side.



• **Figure 30.5** Gillet's test. (From Benzon HT. Pain originating from buttock: sacroiliac joint syndrome and piriformis syndrome. In: Benzon HT, Raja SN, Molloy RE, et al. (eds). *Essentials of Pain Medicine and Regional Anesthesia*. 2nd ed. Philadelphia: Elsevier; 2005).

• **Figure 30.6** Sacroiliac Shear test.

• **Figure 30.7** Thigh Thrust test.

- Comment: This test stresses the SIJC *and* hip joint as well as the posterior elements of the lower lumbar spine. Thus this examination can overlap with intra-articular hip pathology, a more common cause of groin pain, and lumbar facet joint pain, a more common cause of LBP.

  Pelvic distraction Test (Fig. 30.8)
- Position: Prone.

• **Figure 30.8** Pelvic Distraction test.

- Maneuver: The practitioner is facing the patient. The physician placed the left hand over the patient's right ASIS and the right hand over the patient's left ASIS. Firm pressure was applied outward.
- Positive test: Pain over the symptomatic SIJ region (also back, buttock, groin).

  Pelvic compression Test (Fig. 30.9)

• **Figure 30.9** Pelvic Compression test.

• **Figure 30.10** Fortin's Finger test, right side.

- Position: lateral decubitus. Pelvis aligned perpendicular to the floor.
- Maneuver: The practitioner is facing the patient. The practitioner places overlapping hands over the patient's superior ASIS. The firm pressure was applied downward.
- Positive test: Pain over the symptomatic SIJ region (also back, buttock, groin).

Fortin's Finger Test (Fig. 30.10)

- Position: Standing.
- Maneuver: Patient points to their area of maximal tenderness.
- Positive test: If the area of maximal tenderness is greater than the PSIS, this indicates that the SIJC is the source of pain.
- Comment: Is not a part of the actual physical exam but rather the patient's historical account.

Radiographic evaluation of the joint rarely aids diagnosis other than in the setting of trauma or an underlying rheumatologic condition such as spondyloarthropathy (e.g. ankylosing spondylitis). However, using fluoroscopy to assess whether Fortin's point truly overlies the SIJ space has higher sensitivity than physical examination maneuvers alone.[27] X-ray and computed tomography (CT) can show changes to the joint space, bone erosions, subchondral sclerosis, and bony malalignment. Magnetic resonance imaging (MRI) can show intra-articular fluid signal, soft tissue and bone edema, fatty infiltration, and joint erosions, while bone scan can show active areas of increased metabolic uptake. CT has low sensitivity and specificity, and radionucleotide bone scans have low sensitivity but high specificity in patients with positive diagnostic blocks.[28] To date, there have been no studies showing an association between x-ray or MRI findings and pain of the SIJC using a reference standard such as a diagnostic injection,[29–31] but in patients with inflammatory spondyloarthropathies, there is an association between SIJ pathology on MRI, buttock pain, and positive response to nonsteroidal anti-inflammatory drugs (NSAIDs).[32] Diagnostic local anesthetic block of the joint is considered the standard criterion for SI joint pain, although complex innervation patterns and technical limitations prevent it from being considered a gold standard.[6,33,34] Provocation of pain on injection of the SIJ alone is not a suitable criterion for the diagnosis of SIJC as the putative source of buttock pain.[6]

Treatment

In individuals with correctable pathology, such as leg length discrepancy, malalignment, or muscle weakness, addressing the underlying etiology with guided exercise, manual therapy including manipulation, or shoe lifts may be beneficial,[35–37] and there is some evidence supporting medications such as anti-depressants, NSAIDs, and opioids for short-term benefit. However, none have been specifically studied in individuals with SIJC pathology.

Only a handful of prospective studies have evaluated the efficacy of steroid injections for SIJC pain. These studies have shown benefits for both intra-[38] and extra-articular injections,[39,40] but all have been characterized by short-term follow up (≤2 months) and small numbers (<25 patients). Studies that have compared intra- and extra-articular injections have yielded mixed findings,[11–13] suggesting that the injection location should be targeted toward the suspected pain generators (i.e. into the ligaments in young people with suspected extra-articular pathology vs. between the bony interface in older people with arthritis). In individuals with injection-confirmed SIJ pain who fail to derive intermediate- or long-term benefits, placebo-controlled and observational studies indicate that SLBN RFA may provide benefits lasting between six months and one year.[41] Since the lateral branches targeted by RFA innervate the posterior ligaments but not the joint capsule, individuals with extra-articular pathology may be more likely to benefit. This is supported by a study evaluating SLBN RFA outcome predictors whereby older individuals, who are more likely to suffer from arthritis, were more prone to fail treatment.[5]

Arthrodesis has been used for decades to treat SIJC pain resulting from fractures, instability/dislocations, and secondary to degenerative changes. Among these indications, SI joint arthropathy is one of the most controversial, with the available studies being confounded by poor selection criteria, diverse outcome measures, and various forms of bias. Recently, there has been a surge in the use of minimally invasive SIJ fusion techniques to treat individuals who have failed conservative management, with results from observational and prospective randomized trials showing benefits for up to two years.[42]

Technique of Sacroiliac Joint (SIJ) Injection

For diagnostic injections, patients were asked to stop their pain medication on the day of the procedure. Sedation is not recommended by the American Society of Anesthesiologists or Spine Intervention Society[43] and has been shown in a large, randomized crossover study to increase the false-positive rate of diagnostic SIJ injections.[44] Light sedation (low dose intravenous or oral benzodiazepine) may be administered to anxious patients or those with a history of vasovagal episodes. Contraindications to the injection include infection in the area and bleeding diathesis. Allergy (not anaphylaxis) to contrast media may require pretreatment with antihistamines and steroids, whereas allergy to local anesthetics may require identification of the appropriate local anesthetic to be used for the procedure. The use of imaging is recommended during SIJ injection to ensure intra-articular needle placement, as blind injections rarely result in correct needle positioning and may increase the risk of complications.[14,45,46]

Fluoroscopy-Guided SIJ Injection

Fluoroscopy is considered the standard of care for intra-articular SIJ injection, as it detects both intra-vascular and intra-articular needle placement. However, this image guidance modality does not guarantee successful joint access. Therefore more challenging anatomy may require CT guidance.[46,47]

The technique for SIJ injection has been described.[48,49] The target point typically lies along the inferoposterior aspect of the joint, in the area 1 to 2 cm cephalad from its most caudal end.[48]

• **Figure 30.11** Sacroiliac joint injection. Note the spread of the dye along the joint.

Although in individuals with suspected extra-articular pathology, the most painful area may be targeted, such as the cephalad portion of the dorsal ligaments.[50]

Once the needle was within the joint, a small amount of contrast was injected to demonstrate intra-articular spread (Fig. 30.11). The response of the patient to the injection of contrast media is noted as either "no pain," "unfamiliar pain," or "similar pain" than the pain complaint.[6] After appropriate contrast spread, a solution of steroid and local anesthetic is injected. Because the capacity of the SIJ is small and distension may exacerbate pain or rupture the joint capsule, a maximum volume of 2 to 3 mL has been recommended for intra-articular SIJ injections.[48,51] Spillage of injectate outside the SIJ is acceptable because some of the pain receptors are located outside the joint. Some practitioners advocate specifically for intra-articular *and* extra-articular injectate placement because of the known innervation throughout the SIJC, as described above.

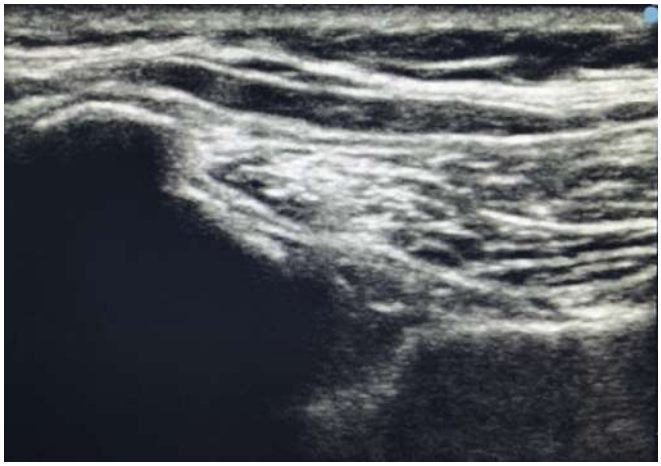
Other approaches include placement of the needle at the inferior end where the posterior and anterior joints overlap if a markedly lucent zone is noted in that area.[48] The midportion of the joint can also be cannulated, although the joint capsule typically extends only about one-third of the way up from the caudad border.[52] Finally, the superior aspect of the joint can be accessed using a cephalo-caudad approach.

After the procedure, the patient should be observed for 15 to 30 min to determine the analgesic response and monitor for complications. The local anesthetic has an immediate effect, but the anti-inflammatory effect of depo-steroid develops over 2 to 5 days, sooner for non-particulate formulations. Guidelines vary regarding the cutoff for designating a block as positive, with some using ≥75% pain relief, others using ≥50%, and still, others advocate an even lower cutoff as the United States Food and Drug Administration and IMMPACT guidelines consider ≥30% pain relief to be a clinically meaningful response.[53,54] Because SI joint pain typically coexists with other musculoskeletal conditions and there is no reliable alternative to treatment, using a less stringent cutoff, such as 50%, as advocated by the international facet guidelines for diagnostic injections, will maximize access to care. Provocative maneuvers can be repeated to assess the improvement. Transient weakness in the ipsilateral leg is because of the spillage of the local anesthetic onto the sacral nerve roots or the SN. Other complications include bleeding, infection, exacerbation of pain, fever, transient difficulty voiding, and allergic reactions to components of the prep solution or injectate.

Ultrasound-Guided SIJ Injection

The feasibility of ultrasound-guided SI joint injections was initially shown by Pekkafahli et al.[55] and was further described by Harmon and O'Sullivan.[56] A curvilinear low-frequency transducer (4 to 6 MHz) was placed perpendicular to the skin over the distal sacrum in the midline in a cross-sectional view (short axis) to identify the sacral hiatus. The probe was moved laterally until the lateral edge of the sacrum came in view and then moved the cephalad to find the medial aspect of the iliac bone. At this site, the SIJ appeared as a hypoechoic wedge-shaped structure (Fig. 30.12). The target area for injection was at the level of the second sacral foramen, which was approximately 2 to 3 cm above the caudal pole of the SI joint. A 22 gauge needle was inserted and advanced in-plane with a lateral and anterior trajectory into the joint. Pop is felt once the synovial joint penetrates. The visible spread of injectate outside the joint indicates periarticular rather than intra-articular placement.

The accuracy of this technique was also assessed. Klauser et al. evaluated ultrasound-guided SIJ injection in cadavers at two levels of the joint by comparing approaches at the level of the first sacral foramen versus those at the second sacral foramen.[57] CT examination showed 90% of the needles at the lower level to be within the SIJ versus 70% at the upper level. The same procedure resulted in an intra-articular placement rate of 100% in both locations (eight in the lower and two in the upper site) when performed in live patients. Jee and colleagues showed an improved ability to avoid intra-vascular structures but a lower intra-articular accuracy rate (87%) with ultrasound versus fluoroscopy (98%).[58] De Luigi et al. found 48/50 (98%) of ultrasound injections to be intra-articular with fluoroscopic confirmation,[59] while Perry et al. found 15/17 (88%) to be intra-articular based on cadaveric dissections.[60] Successful ultrasound injection may be largely related to factors such as body habitus and practitioner experience; for example, Pekkafahli et al. noted marked improvement with operator experience, from a 60% success rate in their first 30 injections to a 94% success rate in their second 30 injections.[55] The successful placement of ultrasound-guided SIJ injections has not



• **Figure 30.12** Ultrasound visualization of the left SIJ. *White arrow*, Ideal needle trajectory; *SIJ*, sacroiliac joint. (Credit: Ariana Nelson, MD.)

been universal. One cadaveric study by Stelzer et al. showed a significantly higher rate of intra-articular injections with fluoroscopy versus ultrasound.[46]

Computed Tomography-Guided SIJ Injection

Injection of the SIJ has been described under CT guidance.[61–63] Success rates from CT-guided injections range from 75% to 92% in the literature.[61,63] The increased radiation exposure and lack of availability of CT in pain clinics restrict the wider application of this approach.

Palpation-Guided SIJ Injection

Palpation-guided intra-articular injections have been shown to be extra-articular in most cases, with one study finding that contrast spread was more likely to be epidural than intra-articular.[45,64,65] In three studies that examined the accuracy of landmark-guided injections, the range for intra-articular spread was between 8% and 22%.[14,45,64] Yet, landmark-guided injections have been reported to result in good pain relief in uncontrolled studies.[66] In a large, randomized, double-blind study by Cohen et al., landmark-guided injections were associated with comparable benefits to fluoroscopically guided injections at one month. However, three months intra-articular injections at three months were superior in some outcome measures.[14] However, some complications were more frequent in the landmark-guided group, and the generally positive results might not be generalizable to a primary care provider population. Palpation guidance cannot be recommended for diagnostic purposes and should not be routinely utilized for therapeutic purposes.

Efficacy and Effectiveness of SIJ Injections

The effectiveness of SIJ injections has been examined in studies, meta-analyses, and reviews with a discordant interpretation of results (Table 30.2).[2,67] Four controlled trials have investigated corticosteroid SIJ injections; all demonstrated some degree of benefit.[38–40,67]

TABLE 30.2 Efficacy and Effectiveness of Sacroiliac Joint Injections

Author	Study Design	Treatment	Results	Comments
Patients With Spondyloarthropathy				
Explanatory studies				
Maugars et al.[38]	Randomized, controlled, double-blind trial (n = 10), patients with spondyloarthropathy	Intra-articular SIJ injection with cortivazol versus placebo (fluoroscopically guided)	At one month, the pain score decreased 5.3 points in the treatment group, 1.8 points in the placebo group; relief lasted six months in 67% of patients	
Observational studies				
Bollow et al.[61]	Prospective case series (n = 66), patients with spondyloarthropathy	Intra-articular SIJ injection with 40 mg depot corticosteroid (CT-guided)	92% had a significant decrease in pain score (from 8.8 to 3.3) at 1.7 weeks; duration of relief ten months	Follow up period up to 18 months
Braun et al.[68]	Prospective case series (n = 30), patients with spondyloarthropathy	Intra-articular SIJ injection with 40 mg triamcinolone (CT-guided)	83% had improvement in pain at 5.2 months (VAS from 8.5 to 3), duration of relief 8.9 months	Follow up period up to 18 months
Fischer et al.[69]	Prospective case series (n = 56), children with juvenile spondyloarthropathy without response to NSAIDs	Intra-articular SIJ injection with 40 mg triamcinolone (CT-guided)	88% had a significant decrease in pain (VAS from 6.9 to 1.8), duration of relief 12 months	Follow up period of 20 months
Patients Without Spondyloarthropathy				
Pragmatic studies				
Luukkainen et al.[39]	Controlled, double-blind trial (n = 20)	Periarticular SIJ injection with 60 mg methylprednisolone + lidocaine versus saline + lidocaine	Improvement in pain score and physical exam in steroid group at two months	
Luukkainen et al.[40]	Controlled, double-blind trial (n = 24)	Periarticular SIJ injection with methylprednisolone + lidocaine versus saline + lidocaine	Improvement in pain score and physical exam in steroid group at one month follow up	
Kim et al.[67]	Randomized, controlled, double-blind trial (n = 48)	Intra-articular SIJ injection with 40 mg triamcinolone versus 25% dextrose	No significant difference in improvement in NRS at two weeks	

Continued

TABLE 30.2 Efficacy and Effectiveness of SIJ Injections—cont'd

Author	Study design	Treatment	Results	Comments
Observational studies				
Lilliang et al.[71]	Prospective case series (n = 39)	Intra-articular SIJ injection with 40 mg triamcinolone (fluoroscopically guided)	67% had 50% relief for over six weeks, the average duration of relief was 37 weeks	SIJ pain diagnosed by a positive response to dual SIJ injections; history of lumbosacral fusion predicted short duration of relief
Chou et al.[4]	Retrospective case series (n = 54)	Intra-articular SIJ injection with 12 mg betamethasone and anesthetic	28% of patients had ≥80% pain relief at two weeks	Dual diagnostic blocks with ≥80% pain relief as diagnostic criteria
Laslett et al.[22]	Prospective case series (n = 58)	Intra-articular SIJ injection with 40 mg triamcinolone and anesthetic	67% of patients had 50% pain relief at six weeks	Dual diagnostic blocks with ≥75% pain relief as diagnostic criteria
Irwin et al.[100]	Retrospective case series (n = 42)	Intra-articular SIJ injection with 80 mg methylprednisolone or 6 mg betamethasone and anesthetic	43% of patients had ≥50% pain relief at one month	Dual diagnostic blocks with ≥70% pain relief as diagnostic criteria
Borowski et al.[11]	Retrospective chart review (n = 120)	Intra-articular injection of local anesthetic and steroid versus intra-articular *and* extra-articular injection of local anesthetic and steroid	At three months, 13% of the intra-articular subgroup and 31% of intra-articular and extra-articular subgroup had a >50% drop in VAS or described ADLs as "greatly improved"	
Murakami et al.[12]	Prospective, unrandomized, case series, n = 50	25 patients with intra-articular SIJ injection of 2% lidocaine, 25 patients with extra-articular SIJ injection of 2% lidocaine	Improvement rate of 96% in the extra-articular group and 62% in the intra-articular group by the Japanese Orthopedic Association "restriction of activities of daily life" scoring system	There was no steroid used in either injection, and longer term improvement was not assessed
Hartung et al.[13]	Prospective, unrandomized, case series, n = 14 (20 SIJs), patients with MRI confirmed active sacroiliitis	20 SIJ injections with steroid and gadolinium performed under ultrasound	At 28 days, no clinically significant difference in the groups was seen, though a significant decrease of mean NRS was seen on both groups (NRS decrease of 2.5 in both groups)	60% of SIJ injections under ultrasound were not positioned within the intra-articular space as confirmed with MRI post-gadolinium

ADLs, Activities of daily living; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *NRS*, numeric rating scale; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SIJ*, sacroiliac joint; *VAS*, visual analog scale.

Multiple uncontrolled studies have also indicated that corticosteroid SIJ injections can provide clinically meaningful pain reduction in patients with and without spondyloarthropathies.[61,68–74]

Techniques of Denervation of the Nerves of the SIJC

Blockade of the L4 medial branch nerve, L5 dorsal ramus, and lateral branch nerves of S1-S3

As noted, the posterior margin of the SIJ and posterior ligaments are innervated by the L5 dorsal ramus and the lateral branches of S1, S2, and S3, with contributions from S4 in some people, and infrequently from L4 (i.e. during sacralization of L5). Because the lateral branches innervate the posterior ligaments but not the joint capsule or ventral ligaments, they cannot be considered diagnostic. However, they are often employed to predict response to radiofrequency (RF) ablation of the same nerves.[75] In two successive studies, Dreyfuss et al. showed that multi-site multi-depth blocks were superior to single-site, single-depth blocks in response to experimental pain provocation of the dorsal ligaments and posterior SIJ capsule.[76,77]

The technique of blocking the L4 medial branch nerve, L5 dorsal ramus, and-S1-S3 lateral branches has been described.[75,77] The patient is instructed to engage in their normal activities and maintain a pain diary to monitor pain relief. In instances where

a dual block paradigm is used, the second block is typically performed with a different anesthetic than the first block to assess the duration of anesthesia that is concordant with that expected (i.e. shorter with lidocaine than bupivacaine, in general). Local coverage determinations may dictate the necessary pain relief to progress to RF lesioning, but 50% to 80% relief is a common threshold because of frequent concomitant pain generators and the inability to target the joint capsule or ventral ligaments.

Radiofrequency Denervation of the SIJC

Transient pain relief from intra-articular steroid injections may require permanent denervation of the nerve supply of the SIJC. Although chemical neurolysis with phenol can be performed, such intervention is rarely used because of possible leakage of the agent with unintended neurolysis of adjacent neural structures, as previously described, the SIJ communicates with the S1 and S2 foramina in a proportion of individuals, and there may also be defects in the anterior capsule that allow direct communication to the region of the lumbosacral plexus. RF ablation of nerves results in controlled and predictable neurolysis.

Complete pain relief after lesioning of the lateral branches at the posterior aspect of the SI joint is unlikely because innervation of the ventral aspect of the joint is not destroyed. However, the posterior aspect of the joint is a more frequent source of pain than the ventral aspect, and numerous investigators have carefully delineated the predominant dorsal innervation of the SI joint.[33,50,78]

The dorsal ramus of either strip lesioning or the periforaminal technique, the dorsal ramus of L5, should be lesioned, in addition to the lateral branches of S1-3 and potentially S4. An RF cannula was placed at the lateral margin of the superior articular process, where it met the sacral ala, as described previously. Because the lesion created by conventional RF is smaller and positioned along the active tip of the probe, the needle trajectory should ideally be oriented nearly parallel to the path of the nerve to maximize the chances of neural destruction when using conventional RF. On the lateral fluoroscopic image, the needle tip should be no further anterior than the anterior third of the superior articular process (SAP).[48] When using cooled RF, the electrode should be inserted in a perpendicular fashion. Internally cooled electrodes result in larger, more circular lesions, and the tip should be situated no more anterior than the midpoint of the SAP to avoid lesioning the segmental nerve root.[79] It has previously been argued that conventional RFA of the L5 dorsal ramus could be safer than water-cooled RFA, but this is speculative. This was investigated by Kapural et al., who retrospectively reviewed 100 cases of RF ablation of the SIJ.[80] Among these patients, 82 had cooled RF of the L5 dorsal ramus, whereas others had conventional RF. The rate of acute complications was not higher in the water-cooled RF group, but this sample size was likely too small to effectively evaluate complications.

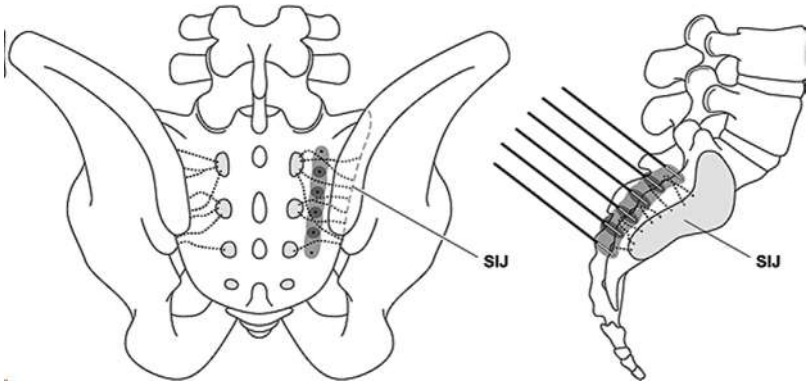
Strip Lesioning of the Sacral Lateral Branch Nerves

RF ablation of the terminal fibers supplying the posterior SIJC (again, contribution from the lateral branches of the posterior rami of S1-S3 +/– L5/S4) can result in analgesia in patients who previously responded to diagnostic SIJC injections.[81] Because the lateral branches targeted for denervation innervate the posterior ligaments, some experts have advocated extra-articular injections,[50] or prognostic multi-site, multi-depth lateral branch blocks[77] as a prognostic tool before RFA. However, studies have found that intra-articular injections may also provide significant predictive value,[82] possibly because of spillover of local anesthetic.

One technique for thermal RF denervation of the dorsal ligament component of the SIJC utilizes two probes to create a bipolar strip lesion.

Although numerous techniques utilizing bipolar lesions have been described, the palisade bipolar strip lesion technique will be outlined here, as it has been shown to capture 100% of the lateral branch nerves 97.5% of the time.[81] In the palisade technique, the patient is positioned prone, and the C-arm is aligned for an anteroposterior image. RF probes (20 g, 10 mm active tip) were placed 10 mm apart in a straight line approximately 4 mm lateral to the lateral border of the posterior sacral foramina from superior to S1 to inferior to S3 (S4 if the inferior border of the SIJ extends caudally beyond S3),[83] and all of the sites were anesthetized with 0.5% 2% lidocaine (Fig. 30.13). In studies where this technique was utilized,[81,83] the RF probe was heated to 90° for 180 s.

Another bipolar strip lesioning technique, referred to as the PSN lateral crest, could be expected to provide similar results to the palisade bipolar technique.[81] In which RF probes are placed along the lateral sacral crest from the first to third sacral tubercles.[84] After all of the sites are anesthetized with 0.5 mL 2% lidocaine, bipolar lesions are created with 17 g two-tined RF probes placed approximately 15 mm apart at 90° for 180 s.[81] This method was originally described for use with ultrasound guidance, and with accurate placement could theoretically provide similar effectiveness



• **Figure 30.13** Palisade treatment of sacroiliac joint (SIJ) pain. A row of straight radiofrequency (RF) cannulae are inserted to contact the dorsal sacral surface perpendicularly between the S1-S3 foramina and the SIJ line. Bipolar RF lesions generated between adjacent cannulae produce a continuous palisade lesion across the region where sacral lateral branch nerves (dotted lines) travel from the sacral foramina to the SIJ. (Left) Needle view. (Right) Lateral view. (From Cosman ER Jr, Gonzalez CD. Bipolar radiofrequency lesion geometry: implications for palisade treatment of SIJ pain. *Pain Pract*. 2011;11(1):3–22.)

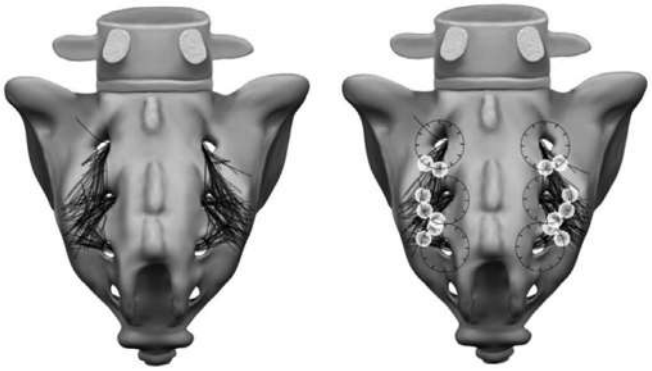
to fluoroscopically guided techniques, although outcomes research is yet to be conducted.

If a monopolar technique[82,85] is utilized, the size of the monopolar lesion can be increased by injecting fluid before the RF lesion is applied.[86] Using *ex vivo* chicken samples, Provenzano et al. noted that pre-injection of fluid other than water increased the lesion size. Hydroxyethyl starch and hypertonic saline resulted in the largest lesions, followed by 0.9% NaCl and lidocaine. Increasing the volume from 0.5 mL to 3 mL did not significantly change the size of the lesion. Similar findings were noted with bipolar lesioning.[87] Three percent NaCl appears to be ideal in that it increases the size of the lesion between the electrodes while diminishing the spread of tissue destruction beyond the electrodes.

Periforaminal Radiofrequency Lesioning of the Sacral Lateral Branch Nerves

Variations of the periforaminal RF technique have been performed with traditional thermal RF[50,75,82,88–90] and water-cooled RF.[5,85,91–93] The water-cooled technique was recently described by Stout et al.[94] With the patient in a prone position, the C-arm is aligned for an anteroposterior image. For the S1-S3 or S4 lateral branches, cooled RF probes (17 g, 4 mm active tip) are placed 10 mm lateral from the center of the sacral foramina, along the dorsal surface of the sacrum at 4:30 and 6:00 for S1; at 2:30, 4:00, and 5:30 for S2; and at 1:00 and 2:30 for S3 on the right; the corresponding mirror targets for the left are at 6:00 and 7:30 for S1; at 6:30, 8:00, and 9:30 for S2; and at 9:30 and 11:00 for S3.[94] Their placement of the RF probes takes into consideration the variability in the course of the nerves and alignment of the posterior sacral foramen vis-à-vis the SIJ and has been shown to capture all medial branches in 95% of SIJC specimens.[81] When the S4 foramen is observed to be at a comparable level in the longitudinal plane to the lowest part of the SI joint (i.e. afferent innervation is likely to be entering the foramen), it may be targeted as well. If the S4 foramen is caudal to the inferior aspect of the ipsilateral SIJ, there is likely little utility in performing a periforaminal lesion (Fig. 30.14). On lateral fluoroscopic images, the needle tip should not be anterior to the posterior sacrum to avoid intra-foraminal positioning. For the L5 dorsal ramus, motor stimulation was applied at 2 Hz at 2 V to verify the absence of muscle contraction in a radicular distribution (motor stimulation is not required for the sacral levels). All of the sites were anesthetized with 2% lidocaine (0.5 mL), and lesioning began at 60°C for 150 s (water-cooled RF). It is often customary to inject 0.5 mL of a mixture of local anesthetic and steroid after the lesioning for postoperative analgesia and prevent neuritis.

In a cadaver study, Roberts et al. showed that bipolar and water-cooled RF lesions captured 100% of the known course of the lateral branches with the greatest frequency, up to 97% and 92% of the time, respectively. In contrast, conventional monopolar was only able to capture 100% of the known course of the lateral branches approximately 12% of the time.[81]



• **Figure 30.14** The figure on the *left* shows the course of the sacral lateral branches as determined by cadaveric study. The figure on the *right* shows all lateral branches from all specimens with clockface overlay and an 8 mm lesion size. (From Stout A, Dreyfuss P, Swain N, Roberts S, Loh E, Agur A. Proposed optimal fluoroscopic targets for cooled radiofrequency neurotomy of the sacral lateral branches to improve clinical outcomes: an anatomical study. *Pain Med*. 2018;19(10):1916–1923.)

Efficacy and Effectiveness of Radiofrequency Denervation of the Dorsal Sacral Nerves and Lateral Branches

The effectiveness of SIJ injections has been examined in studies, meta-analyses, and reviews with somewhat discordant results[95,96] (Table 30.3). Multiple randomized, controlled trials have shown the superiority of RF denervation of the L5 dorsal ramus and the S1-S3 lateral branches over sham procedures.[82,85,91] Water-cooled periforaminal and bipolar RF have been shown to be associated with a higher success rate than conventional monopolar RF.[5,66,81] However, not all studies have shown effectiveness with RF ablation. van Tilburg et al. failed to show the efficacy of conventional RF versus a sham procedure,[89] and Juch et al. failed to show the superiority of conventional RF and exercise therapy to exercise therapy alone,[97] although it should be noted that procedural and methodologic shortcomings in both studies have questioned the validity of the results.[98,99]

Coccydynia

Epidemiology and Etiology

Coccydynia, defined as pain in the region of the coccyx, is an infrequent cause of buttock pain with poorly characterized and underreported epidemiology.[108] Thus its prevalence is thought to be low. Women are more likely to be affected than men, and the prevalence is highest in middle-aged women.[109] Obesity and complications or instrumentation during childbirth are also associated with coccydynia.[108,110–112] Trauma is commonly associated with tailbone pain,[111,113] while ankylosing spondylitis[114] and tumors of the bone or pelvis[115,116] are less commonly reported. Maigne et al. reported that 69% of 208 patients with chronic coccydynia reported a history of prior trauma. Within that series, bony outgrowths, anterior and posterior subluxation, and hypermobility were all identified as predisposing conditions.[111] Minor trauma, such as prolonged sitting on hard or irregular surfaces, may be a predisposing factor.[117] Radicular or visceral pain may also contribute to referred pain in the region of the coccyx.

Anatomy

The coccyx is a small but complex structure located at the distal end of the sacrum, connected to the sacrococcygeal articulation. It comprises three to five fused bony spinal segments (Fig. 30.15). Anteriorly, the coccyx provides attachments for the anterior sacrococcygeal ligaments and fibers of the levator ani muscle, while posteriorly, the gluteus maximus and posterior sacrococcygeal ligaments attach. Between individuals, there is significant variability

TABLE 30.3 Efficacy and Effectiveness of Radiofrequency Lesioning of the Sacral Lateral Branch Nerves

Author	Study Design	Treatments	Results	Comments
Explanatory Studies				
van Tilburg et al.[89]	Prospective, randomized, controlled, double blinded study, n = 51	Conventional RF of L5 dorsal ramus and cooled RF of S1–4 lateral branches versus sham procedure	No significant difference between groups at three months	SIJ pain confirmed by positive intra-articular block; crossover allowed at three months
Patel et al.[85]	Prospective, randomized, controlled, blinded study, n = 51	Cooled RF of the L5 dorsal ramus and S1–3 lateral branches versus sham procedure	At three months, mean NRS −2.4 in the treatment group and −0.8 in sham, ODI −11 in the treatment group, +2 in sham; effect persisted at nine months	Patients with axial back pain and a positive response to dual lateral branch blocks; crossover allowed at three months
Cohen et al.[82]	Prospective, randomized, controlled study, n = 28	Conventional RF of L4 medial branch and five dorsal ramus and cooled RF of S1–3 lateral branches versus sham procedure	Pain scores improved at one month (2.4 in the treatment group, 6.3 in the sham group); benefit persisted at six months	SIJ pain confirmed by positive intra-articular block; crossover allowed at one month
Mehta et at.[101]	Prospective, randomized, controlled, double blinded study, n = 17	Strip lesion with Simplicity of S1–3 dorsal peripheral nerves and conventional RF of L5 dorsal ramus versus sham procedure	At three months, mean NRS −4.7 in the treatment group and −0.3 in sham. Similar results at six months	SIJ pain confirmed by positive intra-articular block
Pragmatic Studies				
Dutta et al.[102]	Prospective, randomized, comparative, study, n = 30	Pulsed RF of the L4, L5 dorsal rami, and S1–S3 lateral branches versus intra-articular steroid injection	Mean pain relief similar and improvement in ODI in both groups at one month, with significantly greater pain relief with RF at three and six months	SIJ pain confirmed by positive intra-articular block
Juch et al.[97]	Prospective, randomized, controlled study, n = 228	Various techniques of RF at various locations with exercise therapy versus exercise therapy alone	No significant difference in NRS at three months	SIJ pain confirmed by intra-articular injection. Results clouded by methodologic concerns
Martinez et al.[103]	Prospective, randomized, controlled study, n = 60	Palisading bipolar RF (needle distance 1 cm) versus palisading bipolar RF (needle distance >1 cm) versus dual SIJ steroid injections	All groups had ≥ 50% pain reduction at one month. At three months, only both RF groups had ≥ 50% pain reduction. At 12 months, only the >1 cm RF group had had ≥ 50% pain reduction	
Salman et al.[90]	Prospective, randomized, comparative, study, n = 15	Conventional RF of the L4, L5 dorsal rami, and S1–S3 lateral branches versus intra-articular steroid injection	53% of patients in the RF group obtained >50% pain reduction	Unable to analyze the control group because of a small number of participants
Zheng et al.[104]	Prospective, randomized, controlled, n = 155	Palisading bipolar RF versus celecoxib	Mean VAS −1.9 at three months and −2.2 at six months with RF group over the control group	Prior diagnosis of ankylosing spondylitis
Observational Studies				
Stelzer et al.[105]	Retrospective chart review, n = 109	Cooled RF of the L5 dorsal ramus and S1–3 lateral branches	Mean VAS −4.0 at one month with similar results seen at six and 12 months	All patients had positive blocks of SIJ *or* medial/lateral branches

Continued

TABLE 30.3 Efficacy and Effectiveness of Radiofrequency Lesioning of the Sacral Lateral Branch Nerves—cont'd

Author	Study Design	Treatments	Results	Comments
Reddy et al.[106]	Retrospective chart review, n = 16	"Simplicity" conventional RF of peripheral nerves at S1–S4	Mean NRS –4.5 at 12 months	Patients included all had a diagnostic and therapeutic SIJ injection with ≥50% NRS reduction *and* for ≥ six months
Romero et al.[107]	Prospective, observational study, n = 32	Conventional RF of the L5 dorsal ramus and S1–3 lateral branches	Mean NRS –4.6 at six months and –3.7 at 18 months	SIJ pain confirmed by positive intra-articular block
Ho et al.[92]	Retrospective chart review, n = 20	Cooled RF of the L5 dorsal ramus and S1–3 lateral branches	Mean NRS –4.9 at three months, –4.4 at 12 months, and –4.3 at 24 months	SIJ pain confirmed by positive intra-articular block
Stelzer et al.[93]	Retrospective chart review, n = 126	Cooled RF of the L5 dorsal ramus and S1–3 lateral branches	Mean VAS –6.2 in the subgroup with follow up from four to six months, –5.5 in the subgroup with follow up from six to 12 months, and –3.9 in the subgroup with follow up >12 months	SIJ pain confirmed by positive intra-articular block
Gevargez et al.[62]	Prospective, observational study, n = 38	Conventional RF in the dorsal interosseous ligament and of L5 dorsal ramus (CT-guided)	At three months, 13 of 38 patients had no pain, 12 of 38 had substantially reduced pain	SIJ pain confirmed by positive intra-articular block (CT-guided)
Cohen and Abdi [75]	Retrospective chart review, n = 9	Conventional RF of L4, L5 dorsal rami, and S1–S3 lateral branches	Eight of nine patients reported 50% or greater pain relief at the nine month follow up. One of nine had a 40% improvement	All patients had a positive response to diagnostic blocks of L4 and 5 dorsal rami and S1–3 lateral branches
Yin et al.[50]	Retrospective chart review, n = 14	Conventional RF of L5 dorsal ramus and S1–3 lateral branches	Nine of 14 with 60% or greater patient-perceived improvement with >50% decrease in pain scores at six months	All patients had dual positive SIJ steroid injections
Karaman et al.[91]	Prospective observational study, n = 15	Cooled RF of the L5 dorsal ramus and S1–3 lateral branches	At six months, 80% had >50% pain relief, 87% had a 10-point decrease in ODI	SIJ pain confirmed by positive intra-articular block

CT, Computed tomography; *NRS*, numeric rating scale; *ODI*, Oswestry disability index; *RF*, radiofrequency; *SIJ*, sacroiliac joint; *VAS*, visual analog scale.

in structure,[118] and mobility[119] of the sacrococcygeal articulation, as well as dimensions and angulation[120,121] of the coccyx itself.

Sensory innervation of the coccyx is primarily derived from the sacrococcygeal plexus, which originates from the lower sacral nerve roots. Anteriorly, this is comprised of the coccygeal nerves and the ventral rami of S4 and S5, while the dorsal rami of S4 and S5 and the coccygeal nerves contribute to innervation.[122] The sacrococcygeal plexus innervates the following anterior structures: the pubococcygeus muscle, ischiococcygeus muscle, coccygeus muscle, and a portion of the levator ani, external anal sphincter, sacrococcygeal and coccygeal ligaments, sacrococcygeal joint, and coccygeal periosteum. Posterior structures innervated by the sacrococcygeal plexus include the dorsal periosteum, overlying skin, and soft tissue.[122–126]

Sympathetic anatomic innervation from the paravertebral sympathetic trunk contributes to the ganglion impar, located on the ventral surface of the coccyx, and visceral pain from the rectum may refer to this region via nociceptive input from the ganglion impar.[127] Pain from other pelvic viscera may also refer to the coccygeal region via the hypogastric plexus or pelvic splanchnic nerves.[122]

Aside from being the insertion point of muscles, tendons, and ligaments, the coccyx supports pelvic floor and anal function and provides structural support in the sitting position in conjunction with the ischial tuberosities.[108]

Presentation

Coccydynia classically presents as pain in the region of the tailbone, but other aspects of the history may be helpful, including pain with sitting, reclining, defecation, or intercourse.[108] Acute onset after a posterior fall could indicate a traumatic etiology. Tenderness to palpation over the coccyx is often present but not requisite, as pain of radicular or visceral origin can refer to this region. Hypermobility of the sacrococcygeal articulation can be diagnosed via rectal examination. Imaging with plain film radiographs, CT,

• **Figure 30.15** Posterior view of the bony sacrococcygeal junction. *Red arrow*, sacrococcygeal articulation. (From White TD, Folkens PI. Pelvic girdle: sacrum, coccyx, & os coxae. In: TD White, PI Folkens (eds). *The Human Bone Manual*. 1st ed. Burlington, MA: Academic Press; 2005: 241–253.)

or MRI may help in diagnosing fractures, dislocations, cysts (pilonidal, Tarlov), or masses.

Treatment

Conservative treatment of coccydynia can be initiated with mechanical support such as modified wedge-shaped, "U"-shaped, or donut cushions that offload pressure over the tender region. Adjusting seating surfaces and workplace ergonomic changes may also offer benefits. Cold and heat therapies are reasonable options. Pharmacologic therapy with NSAIDs and, to a lesser extent, tricyclic anti-depressants have been studied, but the studies were small and the data inconsistent.[128,129] Topical analgesics have been shown to be beneficial in arthritis but have not been studied directly in this patient population. As in other pain states, opioid therapy should only be considered after the failure of conservative therapy and should be used cautiously outside of the acute phase.

Physical therapies, such as massage, manual manipulation, and modalities have been utilized with varying degrees of success. It is thought that these therapies may relieve pain because of inflammation, muscle spasm, ligament pain, and dislodgement of the coccyx.[108] Maigne et al. compared intrarectal manipulation to shortwave diathermy, with significantly more patients experiencing ≥50% pain relief in the intrarectal manipulation group at one and six months.[130] In 2015, Lin et al. compared extracorporeal shockwave therapy to physiotherapy (short wave diathermy or inferential current) with significantly greater mean pain relief in the former group, but no difference in Oswestry disability index scores at eight weeks.[131]

Regarding interventional procedures, there are a myriad of described treatments of coccydynia, most commonly injection of steroids and local anesthetics. There is no clear consensus on the best target for injection, although it is generally accepted that because of the close proximity of the pelvic viscera anteriorly, fluoroscopic or ultrasound guidance should be utilized. Overall, the body of literature surrounding treating coccydynia is low to very low quality because of small sample sizes and methodologic shortcomings. In 1991, Wray et al. randomized 120 patients to receive steroid injections or manipulation. They reported a mean pain reduction of 60% in the steroid group versus 85% in the manipulation group, and the follow up period was unclear in their report.[132] In a small study of 14 patients, Mitra et al. reported that 50% of patients experienced at least 50% pain relief with steroid and local anesthetic injections over and around the coccyx at three weeks.[133] Pulsed radiofrequency treatment of the posterior coccygeal nerves innervating the coccyx was performed in ten patients with a mean improvement in pain of 75% at six months.[134] A study evaluating thermal radiofrequency ablation of the posterior coccygeal nerves in nine patients reported a mean improvement in pain of 55%, with follow up varying between two months and two years.[135] In this study, conventional radiofrequency ablation was found to be superior to pulsed RF, and those who responded to prognostic blocks fared better than those who did not receive pretreatment local anesthetic blocks.

The ganglion impar, which is the terminal pelvic segment of the sympathetic trunk lying just anterior to the coccyx and accessed via the sacrococcygeal articulation, has also been a target for intervention in patients with pain referred from the pelvic viscera, typically in the setting of malignancy. Gunduz et al. performed ganglion impar blocks in 19 patients, with 95% experiencing ≥50% pain relief at a mean follow up of 17 months.[136] Thermal radiofrequency ablation of the ganglion impar has also been described, with a mean improvement at six months in 10 patients, being 66% for pain and 50% for function.[137] Chemoneurolysis of the ganglion impar has also been described in case reports and small case series, the largest of which showed 73% mean pain relief at four months in 28 patients treated with CT-guided ethanol injections.[138,139] It must be noted that a major potential complication of ganglion impar ablation is anal sphincter incompetence, so a thorough risk/benefit discussion with the patient is imperative.

Neuromodulation has also been used to treat chronic coccydynia. Improvement in pain with stimulation of the sacral nerve roots via the sacral hiatus in the epidural space has been described.[140] Stimulation of the S3 nerve root via the S3 foramen[141] and stimulation of the thoracic dorsal columns,[142] both of which were effective in providing pain relief.

For patients with pain refractory to more conservative measures, surgical coccygectomy is the last resort treatment option. While numerous studies have reported significant benefits of coccygectomy (more than half of all patients in every published study have derived benefit), the majority of these studies were retrospective, observational, and uncontrolled, thus limiting the ability to draw firm conclusions from their results.[135] As with non-operative interventions for coccydynia, the body of literature for surgical intervention is low to very low quality because of small sample sizes and methodologic shortcomings.

Piriformis Syndrome

Epidemiology

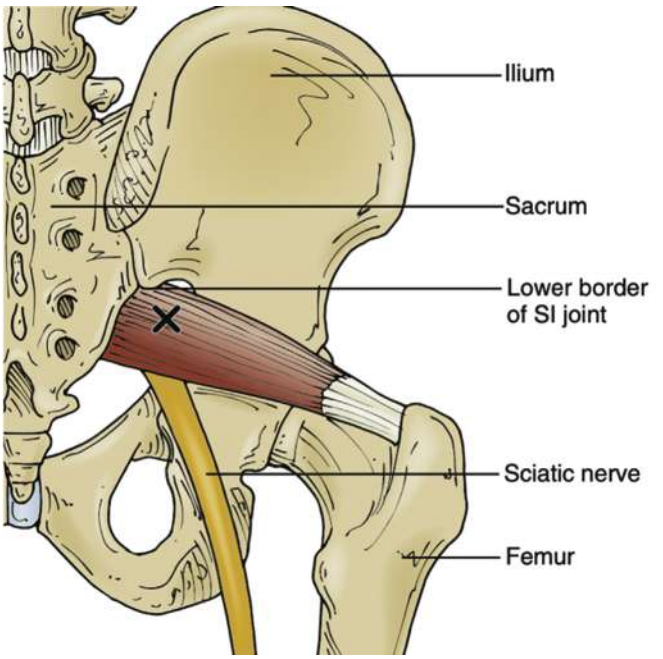
Piriformis syndrome (PS) was first described[143] in 1947 and is relatively uncommon, generally reported as affecting only 5% to 8% of a population. However, the prevalence may be as high as 36% in patients who are referred for back or leg pain.[144–147] It should

be considered in the differential diagnosis of patients who present with unilateral buttock and/or leg pain. However, because its clinical presentation often overlaps with other sources of buttock pain, it is commonly misdiagnosed.[144,147,148]

Anatomy of the Piriformis Muscle and the SN

The piriformis muscle originates from the anterior surface of the S2-S4 sacral vertebrae, the capsule of the SIJ, and the gluteal aspect of the ilium near the iliac spine.[149] The broad origin of the muscle tapers becomes smaller in caliber and tendinous as it courses through the greater sciatic foramen and inserts on the piriformis fossa on the medial aspect of the greater trochanter of the femur (Fig. 30.16). The piriformis is typically innervated by the superior gluteal nerve,[150] and the principal function of the muscle is to abduct and externally rotate the femur. Neurovascular structures close to the piriformis muscle include the posterior femoral cutaneous nerve, gluteal nerves, gluteal vessels, and the SN, most relevant to our discussion.[151]

Formed from the ventral rami (L4-S3) of the lumbosacral plexus, the SN is approximately 2 cm in diameter as it exits the pelvis via the greater sciatic foramen. This large mixed nerve contains motor fibers that supply the posterior thigh, hip, and knee, and sensory fibers that supply the entire surface of the leg distal to the knee, except for the anteromedial calf and medial aspect of the foot.[151] Typically, the SN passes inferior to the piriformis muscle, but deviations in this anatomic relationship are relatively common, and prevalence rates have been described as 6% or up to 22%.[152–155] The Beason and Anson classification system[156] describes these six possible anatomic relationships between the piriformis muscle and the SN (Table 30.4). According to a recent study, the prevalence of the most common relationship types A (the entire SN passes inferior to the piriformis muscle), B (the SN is split, with a portion piercing the piriformis and a portion passing inferior to the muscle), and C (the SN is split, with a portion passing superior to and a portion passing inferior to the piriformis) were 74%, 22%, and 3%, respectively (Fig. 30.17).[157] Anatomic variants are thought to increase the likelihood of developing PS, given that an abnormal course of the SN or smaller divisions would be more susceptible to compression or irritation from muscular hypertrophy than a large-caliber undivided SN.[152,158,159] Indeed, variability in morphometric measurements of the lower limbs correlates with anatomic variations in the relationship of the piriformis muscle with the SN.[144] However, the significance of variant anatomy regarding the likelihood of developing PS is disputed, given the results of a cadaveric surgical case series and a prospective MRI study on living patients,[160] both of which showed similar rates of aberrant anatomy in patients with or without symptoms of PS.



• **Figure 30.16** Posterior view of the sacrum, ilium, and greater trochanter of the femur, illustrating the course of the piriformis muscle, sciatic nerve, and the site of injection (marked "X"). *SI*, Sacroiliac. (From Benzon HT, Katz JA, Benzon HA, et al. Piriformis syndrome: anatomic considerations, a new injection technique, and a review of the literature. *Anesthesiol*. 2003; 98:1442–1448.)

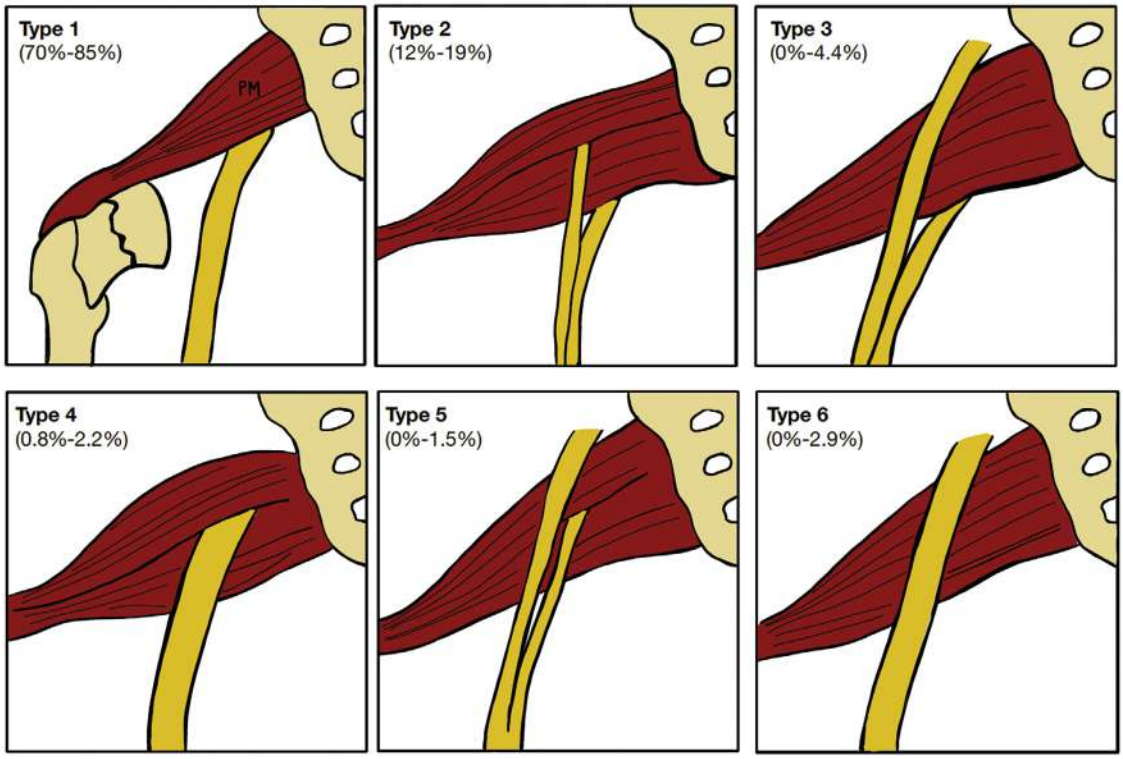
TABLE 30.4 Beason and Anson Classification for the Anatomic Relationship between the Sciatic Nerve (n.) and Piriformis Muscle (m.)

Beason and Anson Classification		
Normal anatomy	Type 1	Undivided sciatic n. passes inferior to undivided m
Proximal division	Type 2	One division passes through, and one inferior to m
Aberrant route	Type 3	One division passes inferior and one superior to m
	Type 4	One division passes inferior and one superior to the m
Normal division	Type 5	Sciatic n. passes through the m
Aberrant route	Type 6	Sciatic n. passes superior to the m

Pathophysiology

The clinical presentation of PS likely has a somatic component, from myofascial pain in the buttock musculature, and depending on the relationship between the muscle and nerve, in some cases, a neuropathic component is present from irritation or compression of the SN. Affected patients had a median age of 50,[161] and females were more affected than males. Risk factors for PS include pelvic/buttock trauma,[147] hypertrophy or spasm of the piriformis or gemelli muscles,[149] female sex assigned at birth, pregnancy, anatomic variants in the relationship between the piriformis and SN, true or apparent leg length inequality (at least 0.5 inches in difference),[154] obesity, hypertonicity, lumbar hyperlordosis, infection, and mass effect from space occupying lesions.[161]

Although a history of trauma can be elicited in 50% of cases of PS,[162] trauma isolated exclusively from the piriformis muscle is rare. Instead, the reported injury is generally mild and deemed to be a sequela of heavy manual labor or strenuous athletic activity that often occurs several months prior to the onset of pain. However, the pathophysiologic relationship between physical stress and muscle pain that occurs months later is debatable. Because of diffuse muscular involvement, some authors now favor the



• **Figure 30.17** Beason and Anson types for the relationship of the piriformis muscle and the sciatic nerve. (Credit: Sophie Sha.)

term "deep gluteal syndrome" rather than PS.[163] However, both terminologies describe a syndrome in which trauma leads to the release of inflammatory mediators, including histamine, bradykinin, and serotonin, which then irritates the buttock musculature and/or the SN.[152,164] This irritation then leads to further spasm or inflammation of the musculature in a classic pain cascade cycle that leads to chemical or anatomic irritation of the SN as it passes between the piriformis muscle and the bony pelvis.[165]

Presentation

In a review of 55 studies, the most common features of a patient with PS were:[166]

- buttock pain
- external tenderness over the greater sciatic notch
- aggravation of pain with prolonged sitting
- augmentation of pain with maneuvers that increase tension on the piriformis muscle

Patients with PS tend to describe pain centered on the buttock and extending from the origin of the muscle at the sacrum to the insertion of the muscle on the medial aspect of the greater trochanter.[144,147,152] Pain is often aggravated by prolonged sitting, especially on hard surfaces or with motor activity involving the affected limb, as in driving or biking, and when rising from a seated position.[144,147] Radiation of pain to the ipsilateral distal leg is thought to be present if the SN is significantly irritated.[147,152]

Physical examination may reveal pelvic tilt, a palpable spindle-shaped mass in the buttock, and tenderness to external palpation or on pelvic/rectal examination, given the proximity of the piriformis to the lateral pelvic wall. The pain can be aggravated by the Valsalva maneuver or flexion, adduction, and internal rotation (FAIR) of the hip-maneuvers that stretch the muscle. If the hip is flexed over 90°, the piriformis is elongated with external rotation, and thus the heel-contralateral knee maneuver may reproduce pain. However, the use of these physical exam maneuvers is not always reliable.[167]

Although PS is a clinical diagnosis, it is also a diagnosis of exclusion from other sources of buttock pain. Therefore diagnostic modalities such as electromyography (EMG), CT, and MRI may assist in diagnosis. EMG can demonstrate a delay in the patient's H-reflex during the FAIR maneuver compared with the patient's H-reflex in an anatomically neutral position.[168] Patients with PS more consistently have electrophysiologic abnormalities in the peroneal H-reflex (prolongation by three standard deviations for definitive diagnosis)[169] than the tibial nerve H-reflex.[170] Although imaging is often negative, CT and MRI may demonstrate enlargement of the piriformis muscle. Magnetic resonance neurography is a more sensitive modality for detecting signal changes in the SN under a hypertrophied piriformis muscle. However, this imaging modality is not universally available, and most insurance companies do not routinely authorize its use.[171] Lastly, ultrasonographic diagnosis of PS is an emerging technique that is being increasingly utilized. Patients with symptomatic PS will demonstrate increased thickness and cross-sectional area of the muscle than asymptomatic individuals.[172,173]

Treatment

As with most pain syndromes, the initial treatment is conservative. Oral nonsteroidal anti-inflammatory medications (NSAIDs) and muscle relaxants are used to reduce inflammation and muscle spasms, respectively, and can be used in conjunction with a course of physical therapy (PT) to improve therapeutic effects. Conventional PT consists of FAIR of the hip followed by pressure applied to the piriformis muscle.[144,147] Exercises such as hip flexion, adduction, and external rotation (ADD stretch), hip flexion, external rotation,

and adduction (ExR stretch) increase the piriformis length by 30% to 40% compared to conventional PT. Treatment with NSAIDs, muscle relaxants, and PT is successful in 75% to 80% of patients.[174]

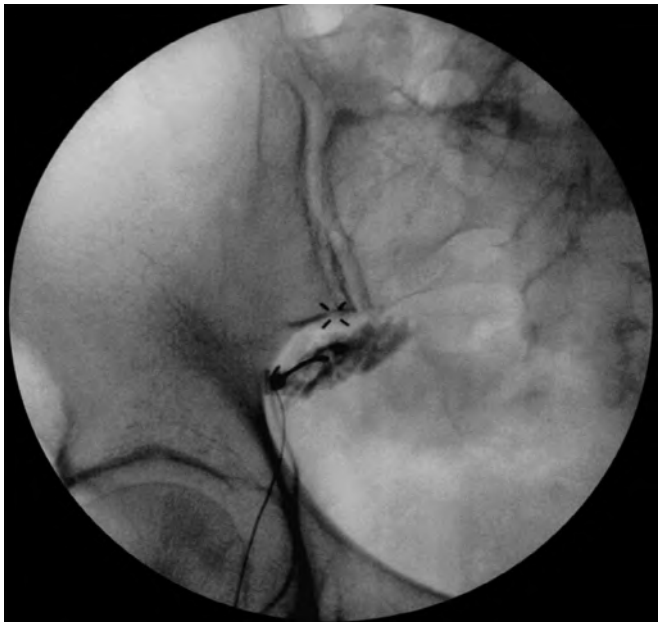
Techniques of Piriformis Muscle and Perisciatic Nerve Injections

The remaining subset of patients are candidates for injection therapy,[175] which can consist of medication administration or dry needling.[176] Injections are typically performed with image guidance, and fluoroscopy, ultrasonography,[177,178] and EMG are often used either alone or in combination.[179] CT and MRI guidance are other options and can better target the tendinous portion of the external rotators of the hip,[180] but their use is infrequent because of increased radiation exposure and logistical difficulties, respectively.

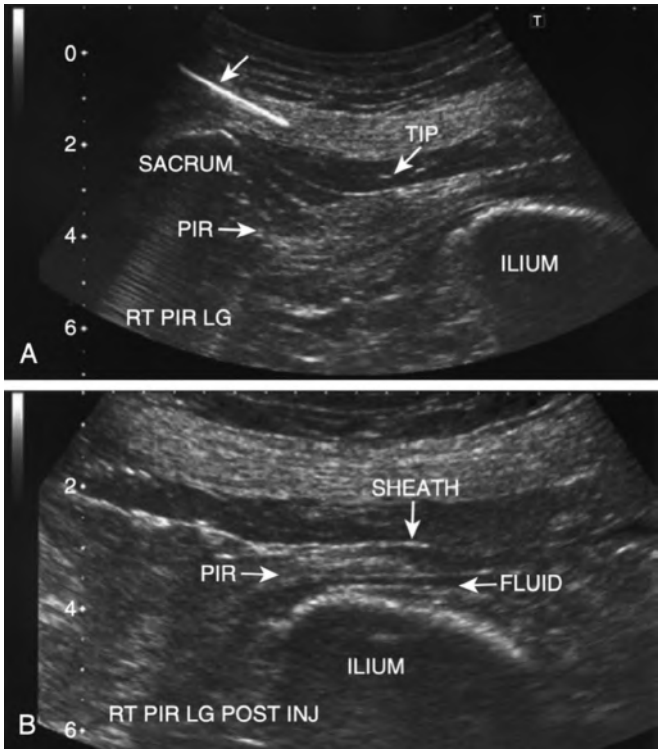
Fluoroscopy is the most commonly used method for image-guided injections. After positioning the patient prone, the needle was advanced coaxially into the muscle belly of the piriformis at 1 to 2 cm lateral and 1 to 2 cm caudal to the inferior border of the SIJ. Contrast dye can then be applied, and if an appropriate myogram is visualized, the injectate is administered (Fig. 30.18).

In addition to fluoroscopy,[152,179] EMG can be used to identify a motor-evoked response from the SN. The needle can then be withdrawn at least 0.3 cm to administer a portion of injectate perisciatically. Then, the needle can again be withdrawn an additional 1 cm to the belly of the piriformis muscle and the remaining injectate administered.[152]

Pain providers offering piriformis injections are increasingly using ultrasound guidance,[181] which is considered more accurate[182] and avoids radiation or contrast exposure. Several ultrasound-guided methods exist, most of which rely on the identification of the inferior/lateral border of the sacrum. Subsequently, the pain providers scanned laterally with the ultrasound probe from the sacral hiatus until the piriformis is identified as a hyperechoic mass deep to the gluteus maximus and an ovoid-shaped SN visible either adjacent to or embedded within the muscle.[177] An alternate approach identifies the PSIS and the posterior inferior iliac spine and then scans inferiorly from the lateral sacrum to the greater sciatic notch plane (Fig. 30.19).[178] Ultrasound can also guide needle placement and the administration of medications, or simply needle placement for dry needling technique.[176,183] Studies have found no difference in pain or satisfaction outcomes when the piriformis is injected with fluoroscopic versus ultrasound guidance.[184]



• **Figure 30.18** Fluoroscopic image of the insulated needle in the piriformis muscle with the muscle being outlined by the injected radiopaque dye.



• **Figure 30.19** **(A)** Longitudinal ultrasound view of the piriformis during needle placement using a medial-to-lateral approach parallel to the long axis of the transducer. The proximal end of the needle has been digitally enhanced to highlight the needle trajectory. **(B)** Post-injection tenogram at the level of the greater sciatic foramen. Anechoic injectate (FLUID) within the piriformis tendon sheath lies superficial and deep to the hyperechoic tendon. *RT PIR LG*, Right side, piriformis, longitudinal view; *TIP*, needle tip. (From Smith J, Hurdle MF, Locketz AJ, et al. Ultrasound-guided piriformis injection: technique description and verification. *Arch Phys Med Rehabil*. 2006;87:1664–1667.)

The injectate is typically composed of a particulate steroid formulation combined with a local anesthetic. In a randomized, double-blind study performed in 47 patients with PS, there was no difference in pain scores up to three months after injection in patients who received local anesthetic only versus local anesthetic with steroid.[185]

Patients may also receive botulinum toxin if the response to steroids and local anesthetics is transient. The use of botulinum toxin to treat refractory PS is supported by randomized controlled and observational studies.[186] The toxin blocks the release of acetylcholine at the neuromuscular junction, resulting in prolonged relaxation, which causes increased fatty infiltration of the piriformis and concomitant reduction in thickness and volume of the muscle.[171,187] The duration of the effect depends on the rate of neuromuscular sprouting and reinnervation of the muscle. However, botulinum toxin typically confers relief for greater than six weeks[188] and lacks the side effects of steroid administration, making it an attractive alternative injectate. Risks of botulinum injection include plexopathy, polyradiculoneuritis, and local psoriasiform dermatitis.[189–191]

The most invasive option for the management of PS includes surgical release, in which the distal piriformis tendon is resected

at the femoral insertion site to decompress the SN. Other musculature of the buttocks can compensate for the loss of this muscle function, and surgery has become less invasive with advances in technique[192] surgical management is effective in approximately 75% of patients.[193] If symptoms recur, they are typically because of incomplete tendon release or scar/hematoma formation.[194]

Non-Piriformis Muscle Pain

Pathology involving muscles besides the piriformis may present as low back and/or buttock pain. Mechanical pain involving muscles and other soft tissue in the buttock may manifest as a dull, aching pain worsened by weight bearing, activities, and sometimes sitting. Depending on the source of pain and the anatomic location of the SN in relation to the structure, patients may also experience true sciatic neuropathy, or "pseudo sciatica," which presents as pain extending into the posterolateral thigh region.

There are reports of pain derived from the gemelli-obturator internis muscle complex, which consists of the obturator internis muscle and bursa, superior and inferior gemelli, and the tendinous insertion of the complex on the greater trochanter. The obturator internis originates from the pelvic surface of the obturator membrane and the surrounding bones. The superior and inferior gemelli originate from the ischial spine and tuberosity, respectively, and are inserted on the medial aspect of the greater trochanter after merging with the tendon of the obturator internis. Pain arising from the gemelli-obturator complex may manifest as an aching pain in the retrotrochanteric region that extends into the hip and posterolateral thigh.[195,196]

In some individuals, movement may bring the SN into juxtaposition with the obturator-gemelli complex (i.e. tendon). An anatomic study performed in cadavers and human volunteers showed that internal rotation of the hip could result in deviation of the nerve course, causing symptoms of sciatic neuropathy.[195,197]

Tendonitis, muscle tears, and spasms of the quadratus femoris can manifest as buttock pain, groin pain, hip pain, and "sciatica," depending on the anatomic relationship with the SN or its branches.[198–200] The gluteal muscles and their tendinous insertions are also a potential source of buttock and lateral hip pain.[201–203] The gluteus maximus, which extends and laterally rotates the hip, is the largest muscle in the buttock-hip region, originating from the sacrotuberous ligament and inserting into the iliotibial band. The gluteus medius muscle arises from the ilium, attaches to the lateral greater trochanteric, and functions to stabilize the femur and pelvis during weight bearing. Pathology of the gluteus minimus, which originates from the external iliac fossa and inserts on the anterior facet of the greater trochanter, most often occurs in conjunction with disorders involving the gluteus medius tendon. The gluteus minimus is involved in internal hip rotation and abduction. For muscles, activities that involve their function may exacerbate pain from overuse injuries, while activities that stretch the muscles may worsen pain arising from muscle spasms.

The treatment of muscle pain depends on the pathology and may consist of rest for overuse injuries, stretching exercises for muscle spasms, PT and exercises to address biomechanical precipitating factors, and nonsteroidal anti-inflammatory drugs for inflammatory processes. Injections have also been employed for both diagnostic and therapeutic purposes.[199,204] In refractory cases of SN entrapment, surgical decompression may be indicated.[198]

Trigger point injections may be considered when myofascial pain is suspected. This concept and technique are discussed in Chapter 68. For non-piriformis trigger point injections, studies have found greater short-term benefit with the injection of substances than dry needling, with little difference in outcomes between injectates.[205,206]

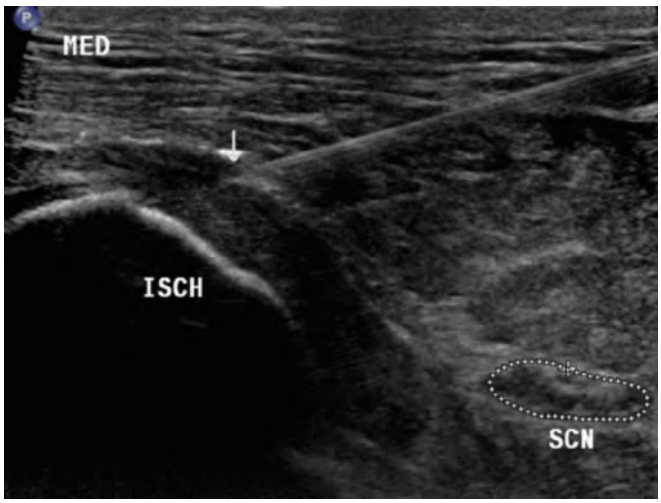
Ischial Bursitis

In ischial bursitis, also termed ischial-gluteal bursitis, the fluid-filled sac (the non-pathologic bursa contains minimal fluid) that separates the ischial tuberosity from the gluteus maximus muscle becomes inflamed. Although the epidemiology is unknown, it is estimated to account for less than 1% of cases of low back or buttock pain. Risk factors for ischial bursitis include obesity, autoimmune diseases, excessive or inappropriate exercise, and a sedentary lifestyle characterized by long periods of sitting; hence, the colloquial nickname "weaver's bottom."[207] The typical presentation of ischial bursitis is gluteal or upper posterior thigh pain, often provoked or exacerbated by exercise or prolonged sitting. On physical examination, tenderness to palpation was a prominent objective sign. MRI can be helpful in the diagnosis and may show low or intermediate signal intensity on T1 and T2 hyperintensity in the region of the ischial bursa.[208] The treatment of ischial bursitis is symptom-oriented and may include ergonomic modification, PT, NSAIDs, and steroid injections.[209] Surgical resection of the bursa may be performed for refractory cases.[210]

Techniques of Ischial Bursa Injection

Ischial Bursa Injection Under Ultrasound

The patient was positioned in the contralateral decubitus position. With an ultrasound-guided injection, the ischial tuberosity was palpated, and a curvilinear probe was placed axially over the ischial tuberosity. In this view, the ischial tuberosity, hamstring tendons, gluteus maximus, and SN can all be visualized (Fig. 30.20). Flexion of the knee and hip decreases the distance between the bursa and skin compared to hip and knee extension. Using a sterile technique, the needle is passed through the skin in an in-plane approach, traversing the gluteus maximus toward the ischial tuberosity. When the needle tip is clearly visualized in



• **Figure 30.20** Ultrasound image demonstrating a needle within the ischial bursa. The gluteus maximus muscle is above the needle tip, and the hamstring tendon origin is below the needle tip. The *arrow* indicates the needle tip; the top is superficial; the bottom is deep; the left is medial *(MED)*, and the right is lateral. *ISCH*, Ischium; *SCN*, sciatic nerve. (From Wisniewski SJ, Hurdle M, Erickson JM, Finnoff JT, Smith J. Ultrasound-guided ischial bursa injection: technique and positioning considerations. *PMR*. 2014;6(1):56–60.)

the region of the ischial bursa, an injectate of local anesthetic and particulate steroid is administered into the bursa.[211]

Ischial Bursa Injection Under Fluoroscopy

A fluoroscopically guided ischial bursa injection was performed with the patient in the prone position and the fluoroscope image intensifier oriented in the cephalocaudad position. A 22 or 25 gauge Quincke needle was introduced perpendicular to the skin on the inferior portion of the buttock and directed in a coaxial fashion toward the ischial tuberosity. After contact with the bone, the needle was withdrawn 1 mm, and contrast dye was administered. If vascular uptake is absent and a fill pattern consistent with a filling of the ischial bursa is noted, then an injectate of particulate steroid and local anesthetic is administered.

Summary Comments

Much like pain in the lower back, pain in the buttock is derived from numerous anatomic pain generators (Table 30.5). When considered as an entity separate from LBP, the benign sources of buttock pain include the SIJ and associated structures, termed the SIJC, the coccyx and associated soft tissues, the deep external hip rotator muscles including the piriformis muscle along with the SN, and other soft tissues of the buttock region. The diagnosis and management of these pain generators differ markedly and are discussed in detail in this chapter.

TABLE 30.5 Presentation of Different Etiologies of Buttock Pain

Condition	Historical Findings	Pain Pattern	Physical Exam Findings	Imaging/Diagnostic Findings
Sacroiliac joint complex pain	Trauma to back or pelvis Spinal deformity Prior spinal surgery Leg length discrepancy Patient points to pain over the PSIS or sacral sulcus May be pain with walking, prolonged sitting, rising from sitting Female gender Onset during pregnancy or childbirth	Pain largely below L5 level Radiation to the groin or posterior thigh to the upper calf	Three or more positive physical exam findings Tenderness to palpation over the posterior joint, PSIS, sacral sulcus Absence of neurologic signs	Imaging is typically normal or shows mild osteoarthritis Plain film radiographs and CT may show changes to the joint space, bone erosions, subchondral sclerosis, and bony malalignment MRI can show intra-articular fluid signal, soft tissue and bone edema, fatty infiltration, and joint erosions Radionucleotide bone scan can show active areas of increased metabolic uptake
Piriformis pain	Trauma to pelvis or buttocks Overuse (athlete, laborer) Leg length discrepancy Pain with prolonged sitting, particularly on hard surfaces, or rising from a seated position	Pain in the buttocks radiating to the greater trochanter If the sciatic nerve is irritated, radiating pain down the posterior ipsilateral thigh	Tenderness to palpation in the buttocks; may have a palpable tender point Provocative maneuvers include hip flexion, adduction, and/or internal rotation Numbness in the ipsilateral leg is rare Normal reflexes	MRI may show an enlarged piriformis, the relationship of the muscle to the sciatic nerve, or localized inflammation CT may show traumatic sequelae, pelvic visceral or soft tissue masses EMG - fibular H-reflex may be prolonged
Coccydynia	Trauma to the tailbone Prolonged sitting on hard surfaces	By definition, pain is in the area overlying or immediate to the coccyx Pain may be vague if referred from the pelvic viscera or sacral nerve roots	Tenderness to palpation over the coccyx or sacrococcygeal junction Hypermobility of the coccyx on rectal exam Dislodgement of the coccyx	Plain film radiographs, CT, or MRI, may help in diagnosing fracture, dislocation, cysts (pilonidal, Tarlov), or masses
Ischial bursitis	Exacerbated by prolonged sitting ("weavers bottom"), or exercise Might be concomitant with obesity, sedentary lifestyle, or autoimmune disease	Pain in the lower buttocks over the ischial tuberosity Proximal posterior thigh pain	Tenderness to palpation over the ischial tuberosity Pain with end-range hip flexion	Ultrasound may show fluid within the bursa MRI may show bursitis or proximal hamstrings/gluteal tendinopathy
Non-piriformis muscle pain	Dependent on the structure(s) involved: may be pain with activity, weight bearing, or sitting Trauma to the gluteal region	Dependent on the structure(s) involved: pain may be in the deep or superficial gluteal musculature, at the attachments on the greater trochanter, radiation into the hip or lateral thigh. If the sciatic nerve is irritated, radiating pain down the posterior ipsilateral thigh	Dependent on the structure(s) involved: may exhibit tenderness to palpation of the deep or superficial gluteal musculature over the posterior or greater trochanter May exhibit pain with internal rotation or hip flexion	Ultrasound may show tendinopathy or hematoma Plain film radiographs and CT may show fracture MRI may show tendinopathy or another soft tissue injury

CT, Computed tomography; *EMG*, electromyography; *MRI*, magnetic resonance imaging; *PSIS*, posterior superior iliac spine.

Key Points

- The causes of pain localized to the buttocks are diverse and often challenging to diagnose.
- The SIJC consists of the SIJ and anterior and posterior stabilizing ligaments. The sensory innervation of these structures is complex.
- The SIJC pain is felt in the SIJ area and can radiate to the lateral hip, posterolateral thigh, posterior leg, and groin.
- The common tests that confirm the presence of SIJC pain include the FABER-Patrick, Gaenslen, Yeoman, Gillet, sacroiliac shear, pelvic distraction, pelvic compression, and thigh thrust tests.
- The diagnosis of SIJC pain is based on the patient's history, symptoms, physical examination maneuvers, elimination of the other causes of buttock pain, and a positive response to an SIJ injection.
- Relief from the SIJ or SIJ *and* periarticular injection with local anesthetic and steroids can be temporary. More prolonged relief can be obtained by thermal RF lesioning of the SIJ or the lateral branches of the primary ramus of the L5-S3 nerves. The literature supports periforaminal RFA and sacral lateral crest strip lesion RFA techniques as successful methods to relieve pain from the SIJC.
- Coccydynia most commonly occurs after trauma, with women more often affected than men.
- Visceral pain may refer to the area of the coccyx via the ganglion impar, hypogastric plexus, or pelvic splanchnic nerves.
- Interventional treatment for coccydynia can be performed with sacrococcygeal joint injection, radiofrequency ablation of the coccygeal nerves, ganglion impar injection or radiofrequency ablation, and surgery with coccygectomy.
- PS is located in the buttocks and radiates to the ipsilateral hip. It may radiate to the leg if the SN is compressed or irritated.
- Physical examination signs to confirm PS include the Pace, Lasègue, and Freiberg signs.
- The diagnosis of PS is usually based on the presence of the above symptoms and positive provocative tests.
- Perisciatic and piriformis muscle injections of steroids and local anesthetics may result in relief that lasts several months. If the relief is transient, injections of botulinum toxin may provide longer relief.
- Non-piriformis muscle pain may present similar to PS, as an aching pain that worsens with sitting or movements, with or without sciatica, depending on the relationship of the gemelli-obturator muscle complex with the SN.
- Similar to PS, injections may be indicated for diagnostic and therapeutic purposes in individuals who fail to respond to conservative therapy.
- Ischial bursitis, also known as "weaver's bottom," typically presents as an aching pain in the lower buttock region and worsens with sitting or certain activities. Treatments include NSAIDs, ergonomic modification, PT, and steroid injections.

Suggested Readings

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31

Facet Pain: Pathogenesis, Diagnosis, and Treatment

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Introduction (Importance of the Problem)

Low back pain (LBP) and neck pain represent two of the five leading causes of medical disability worldwide. More than 75% of patients reporting spine pain are between 18 and 65 years old, thereby adding to the burden through lost productivity and wages.[1] Although the prevalence of LBP varies greatly throughout the literature, some lifetime prevalence estimates are as high as 84%–90%.[2,3] The five year recurrence rate of LBP may be as high as 69%.[4] The lifetime prevalence rate of neck pain has been estimated to be approximately 67%.[5,6] In 2016, LBP and neck pain expenditures were estimated at $134.5 billion, an increase of 44.4% from 2013.[7]

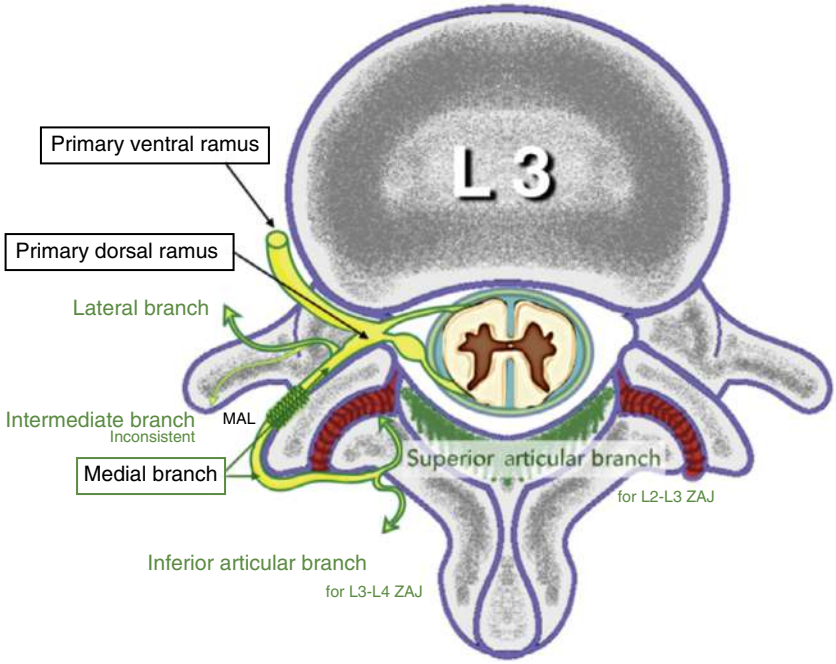
Anatomy and Function

The spine is usually composed of seven cervical, 12 thoracic, and five lumbar vertebrae. The z-joints are paired structures situated posterolateral to the vertebral body. In conjunction with the intervertebral disk, they make up what is commonly known as "the three-joint complex." Together, these joints support and stabilize the spine and prevent injury by limiting motion in all planes. The lumbar z-joints are diarthrodial synovial joints formed from the superior articular process of one vertebra and the inferior articular process of the vertebra above. The volume capacity of these joints is approximately 1–1.5 mL in the lumbar region and 0.5–1.0 mL in the cervical region.[8] The articular surfaces are covered by hyaline cartilage and contain a fibrous capsule. The fibrous capsule is approximately 1 mm thick and forms mostly collagenous tissue arranged in a transverse fashion to provide resistance to forward flexion.[9,10] The superior and inferior joint borders are formed by the fibrous capsule. There is also a small meniscoid structure inside the joint composed of connective tissue rim or adipose tissue.[11] In the lumbar spine, the multifidus muscle serves as the posterior joint border, and the ligamentum flavum replaces the fibrous capsule at the anterior border.[11,12] The position of the joint relative to the sagittal and coronal planes helps determine the role the joint plays in protecting the spine against excessive motion. Joints oriented parallel to the sagittal plane (e.g. upper lumbar spine) provide little resistance to backward and forward shearing forces, but limit excess rotation, flexion, and extension. Joints oriented closer to the coronal plane (e.g. thoracic spine and lower lumbar spine) will allow less rotation, flexion, and extension but protect against shearing forces. The cervical z-joints are inclined at approximately 45° from the horizontal plane and angled 85° from the sagittal plane. This alignment prevents excessive anterior translation and assists the disks in weight bearing.[12,13]

The mamillo-accessory ligament (MAL) is a fibrous connective band that extends from the mammary process to the accessory process (Fig. 31.1).[14] The importance of the MAL lies in the fact that they provide a fibrous tunnel through which the lumbar medial branch of the T12–L4 dorsal rami course.[15] This protects the medial branch but may interfere with nerve anesthetization during medial branch blocks and neurotomy during radiofrequency ablation.[16] The MAL can also become ossified, becoming a hypothetical source of medial branch entrapment, particularly at lower lumbar levels.[17]

The medial branch of the posterior rami supplies sensory and proprioceptive innervation to the facet joint. Each exiting spinal nerve splits into ventral and dorsal rami. The ventral ramus is the largest of the two branches and is the primary source of motor and sensory fibers. The posterior ramus divides into the lateral, intermediate, and medial branches. In the lumbar region, the lateral branch innervates the paraspinal muscles, thoracolumbar fascia, and sacroiliac joint, and supplies variable sensory fibers to the skin overlying the spinous processes. The small intermediate branch supplies the longissimus muscle. The medial branch is the largest branch of the posterior primary ramus and innervates the lumbar z-joint, multifidus muscle, interspinal muscle and ligament, and periosteum of the neural arch. Each medial branch gives rise to an ascending and a descending branch, innervating half of two adjacent z-joints.[12] Therefore to block sensory input from a single z-joint, two adjacent medial branches must be anesthetized.

Facet joints are imbued with rich innervation containing encapsulated (Ruffini-type endings, Pacinian corpuscles), unencapsulated, and free nerve endings.[18] In addition to being a potential pain generator, the z-joint capsule is thought to serve in a proprioceptive capacity as well, as evidenced by the presence of low threshold, rapidly adapting mechanosensitive neurons. In addition to substance P and calcitonin gene-related peptide, a substantial percentage of nerve endings in the facet capsules contain neuropeptide Y, which is indicative of the presence of sympathetic efferent fibers.[19] Nerve fibers have been found in subchondral bone and intraarticular inclusions of facet joints, thus signifying that facet-mediated pain may originate in structures besides the joint capsule.[20] Inflammatory mediators, such as prostaglandins,[21]



• **Figure 31.1** L2 Schematic drawing of the branches of the L2 dorsal ramus. Note that the L2 medial branch participates in the innervation of L2-L3 z-joint and L3-L4 z-joints. *MAL*, Mamillo-accessory ligament; *ZAJ*, zygapophysial joint.

and the inflammatory cytokines interleukin-6 and tumor necrosis factor-α[22] have been found in facet joint cartilage and synovial tissue in degenerative lumbar spinal disorders.[23]

Lumbar Facet Joints

The lumbar facet joints are aligned laterally to the sagittal plane and vary in angle. In an anatomic study published in 1940 by Horwitz and Smith,[24] the authors found that the L4–5 z-joints tended to be more coronally positioned (almost 70° with respect to the sagittal plane), whereas the L2–3 and L3–4 joints were likely to be oriented more parallel (<40°) to the sagittal plane. In posterior studies,[9,25] investigators have found that the upper lumbar facet joints (T12–L2) are oriented closer to the midsagittal plane of the vertebral body (mean range, 26° to 34°), whereas the lower facet joints tend to be oriented away from the plane (40° to 56°). Approximately 80% of the facet joints are curved in the upper lumbar spine and 20% are flat. In the lower lumbar spine, these numbers are reversed.[24] Studies by Grobler and colleagues[26] and Boden and associates[27] found a positive association between degenerative spondylolisthesis and more sagittally oriented lower lumbar facet joints. The inferior articular processes of L5 combine with the superior articular processes of the sacrum to form the L5–S1 facet joints.

Sensory innervation of the facet joints is derived from the medial branches arising from the posterior primary rami at the same level and the level above the facet joint.[8,28] The medial branches of L1–L4 run across their respective transverse processes one level below the named spinal nerve (e.g. L4 crosses the transverse process of L5) and traverse the dorsal leaf of the intertransverse ligament at the base of the transverse process. The nerve then proceeds along the junction of the superior articular and transverse processes, courses underneath the MAL, and splits into multiple branches as it crosses the vertebral lamina (Fig. 31.1). Calcification of the MAL can be a source of nerve entrapment,[29] most commonly occurring at L5 (20%) and L4 (10%). At L5, the dorsal ramus itself is amenable to blockade.[30,31] Some authors have claimed that a branch from the S1 nerve root can run cephalad to supply a portion of the L5–S1 facet joint, although this is controversial.[32,33] It is important to appreciate the distances between the posterior rami proper and the medial branch (since the objective of diagnostic blocks and neurotomy is to target the medial branch selectively). Shuang found that the distance between the branch point of the dorsal ramus and the upper edge of the root of the transverse process (i.e. target point for the medial branch) averaged 3.5 (SD 1.2) mm, 3.6 (SD 1.4) mm, 3.5 (SD 1.3) mm, 3.4 (SD 1.2) mm, and 1.9 (SD 0.9) for L1 to L5, respectively. The L5 distance was significantly shorter than the L1–L4 distance.[34] The extensive spread of local anesthetic in soft tissue (i.e. 0.5 mL covers an area of 6 cm^2) highlights the lack of specificity for medial branch blocks.

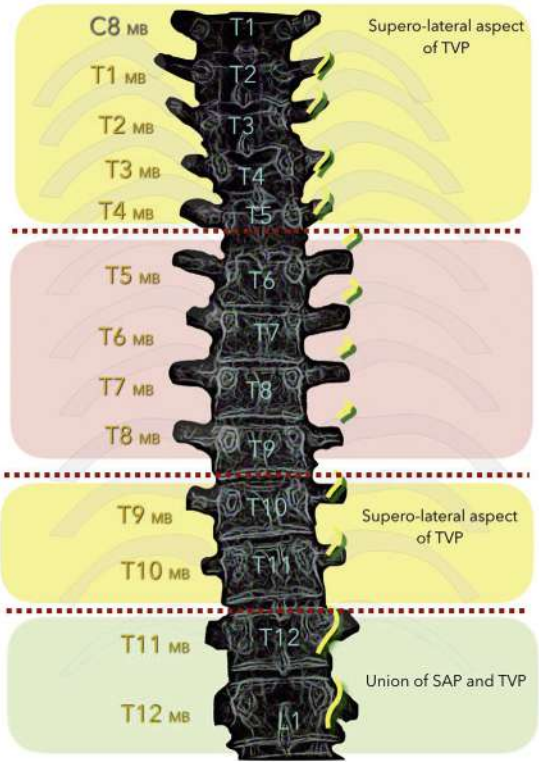
Thoracic Facet Joints

The thoracic z-joints are vertically oriented, with the anterior portion located more cephalad.[9,35,36] The frontal orientation permits lateral flexion at the expense of axial rotation. In the low thoracic spine, the angle transitions from a predominantly frontal orientation to the characteristic sagittal orientation of the lumbar facets. This transition generally occurs between T11–12 and T12–L1.[11,25] A study by Masharawi[13] showed that thoracolumbar facet joints were positioned in an oblique plane. In the transverse plane, facets T1–T11 were positioned with an anterior inclination of approximately 25° to 30° from the frontal plane. The transverse orientation of lower thoracic facet joints is highly variable.[10] Unlike the lumbar facet joints, where tropism is unusual,[9,37] asymmetry is the rule rather than the exception in the thoracic spine, with the right side generally oriented more vertically and frontally than the left.[10] The normal angles of z-joints gradually increase as they transition downwards toward

the lumbar spine by converging to the frontal plane, more so in the sagittal than the transverse plane.[38]

Sensory innervation of the thoracic facets is comparable to that in the lumbar spine, with innervation derived from the medial branch at the same level and level above. Exceptions to this rule sometimes occur at the uppermost thoracic z-joints, whereby the medial branches from C7 and C8 may travel caudad to levels as low as T3.[39] In a cadaveric study by Chua and Bogduk,[40] the authors showed that the thoracic medial branches assume different courses depending on the level. This study asserts that the T1–3 and T9–10 medial branches can be found on the superolateral edge of the transverse process of the subjacent vertebrae (T2–4 and T10–11, respectively). The relationship with osseous structures has implications for treatment. In the mid-thoracic region, the T4–T8 levels contain substantial inter and intraspecimen variability, with facet joint innervation often arising directly from the dorsal ramus rather than the medial branch and frequently traversing the intertransverse space without consistent bone contact.[41]

Because the thoracic medial branches also swing laterally to circumvent the multifidus muscle, motor stimulation of the multifidus muscle cannot be used reliably to confirm needle placement during radiofrequency (RF) treatment. In none of the 84 medial branch dissections did the authors[41] find the nerve crossing the junction between the superior articular process and the transverse process, as occurs in the lumbar spine. Instead, the superolateral corner of the transverse process was noted to be a more accurate target point for diagnostic blockade and denervation (Fig. 31.2). A recent study suggested that the posterior rami in the thoracic spine may send a branch, termed the "descending branch," to the facet joint before the bifurcations of the medial and lateral branches.[42]



• **Figure 31.2** Schematic drawing depicting the theoretical courses of thoracic medial branches. Note that from T1 to T4 and T9 to T10, the medial branches cross the superior lateral quadrant of the transverse process. In the mid-thoracic area, from T5 to T8, there is no consistent relationship between the facet joint nerve supply to any bony structure, so the medial branches appear to be suspended in the intertransverse space.

Cervical Facet Joints

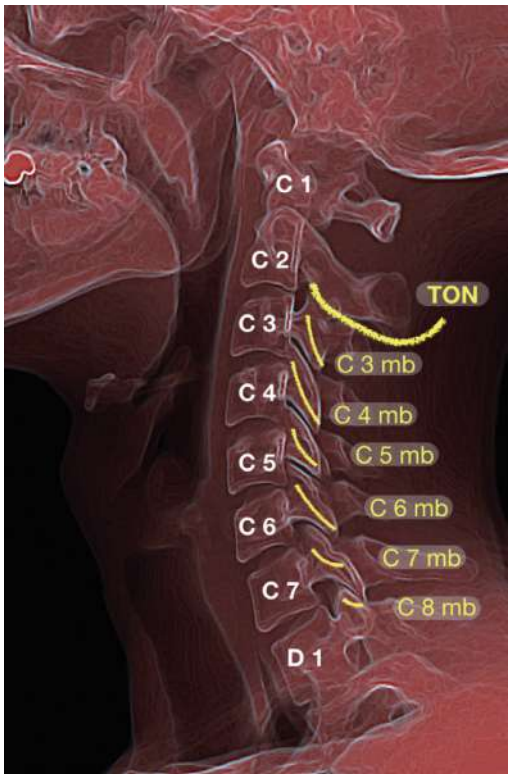
To facilitate the complex motions of the neck, the position and shape of the cervical z-joints change greatly from the base of the occiput to the cervicothoracic junction.[25,43,44] The occiput sits on the C1 articular processes in an orientation nearly parallel to the axial plane. The superior articular process at C3 faces posteromedially, with a 70° angle in the sagittal plane and a 45° angle in the transverse plane. The relative position of the C2–3 facet inhibits rotation and serves to anchor the C2 vertebra as a rotational pivot for the atlantoaxial joint (C1–2). Between C3–4 and C7–T1, the facet joint orientation transitions to the more posterolateral position of the C7 superior articular process. The most frequent site of this transition is the C5–6 joint. The position of the z-joints at this level allows flexion, extension, rotation, and lateral bending. Because of the enhanced mobility of this segment, the C5–6 level is also the most prone to facet dislocations and spondylosis. The shapes of the C3–6 facet joints tend to be round and almost flat, whereas the C6–T1 z-joints are elliptical with a more concave surface. The combination of shape and orientation at the cervicothoracic junction is designed to maximize stability.

Innervation of the cervical z-joints is more complicated than that of the lumbar and thoracic levels. Similar to the lumbar and thoracic z-joints, the C3–4 to C7–T1 facet joints receive dual innervation from the medial branches at the same level and one level above.[45] In some individuals, there are dual medial branches at a single level, which most commonly occurs at C4 and C5. The medial branches curve around the waists of the articular pillars at their respective levels then branch out to supply two joints. The tight fascia and tendons of the semispinalis capitis muscle ensure that the medial branches cling closely to the periosteum, thereby making their position more predictable. In a lateral projection, the medial branches lie near the center of the articular pillars at midcervical levels (Fig. 31.3).[46–48]

The innervation of C2–3 is slightly more complicated. This uppermost facet joint receives the majority of its innervation from the C3 dorsal ramus. The C3 dorsal ramus is normally divided into two separate medial branches. The larger superficial branch is also known as the third occipital nerve, and the inferior branch is termed the deep medial branch. Some innervation of the C2–3 level is also derived from the C2 dorsal rami, which may form five distinct branches, the largest of which is the greater occipital nerve.[48,49] Along with the upper cervical z-joints themselves, the dorsal rami and its branches can be a source of cervicogenic headache.[50,51]

Pathophysiology

Osteoarthritis (OA) is the most important cause of facetogenic pain. In most cases, facet joint arthropathy is a product of years of repetitive strain and low-grade trauma. This is illustrated by the strong association between facet arthropathy and increasing age.[52–56] Studies have demonstrated that intervertebral disk degeneration virtually always precedes facet changes in the lumbar spine.[57] In some cases, an inciting event or pathology can be identified, but the etiologic relationship between the identified inciting event and pain is not always clear. For example, in the lumbar spine, Okonkor et al.[57] found that 52% of 1069 patients with positive lumbar facet blocks



• **Figure 31.3** Schematic drawing of the cervical medial branches (mb). Note how the medial branch of C5 crosses the center of the articular pillar, while branches above and below C5 cross their articular pillars at more cephalad locations.

reported an inciting event, with motor vehicle collisions, sports injuries, and falls being the most common.

Preceding trauma is especially common in the cervical spine, particularly whiplash injuries.[47,51,58] This can result in chronic neck, head, and shoulder pain secondary to hyperflexion and rotation.[59,60,61]

Cadaveric and Laboratory Studies

Ianuzzi and coworkers[62] found that joint moments occurring with any given motion correlate with the magnitude of joint displacement and tend to be greatest at the L4–5 and L5–S1 joints. At the three most caudal joints (L3–S1), contralateral bending was associated with greater capsular strain than ipsilateral bending. In contrast, the L1–2 and L2–3 joints undergo greater strain during ipsilateral flexion. For the upper three facet joints, the maximum joint displacement and the greatest strain were associated with lateral bending. For the two lowest joints, the greatest degree of strain occurred during forward flexion (Table 31.1).

Later work provided evidence that spinal fusion can lead to accelerated degeneration at adjacent levels.[63–67]

The z-joints may respond to repetitive strain and inflammation by filling with fluid and distending, thereby stretching the capsule.[68] Pain from capsular inflammation can spread beyond the joint area because of compression of the exiting nerve root, especially with foramina that are already narrowed by facet joint hypertrophy, osteophytes, or herniated intervertebral disks.[69–72] Inflammatory cytokines released from facet joint tissue may also contribute to the radicular symptoms in patients with spinal stenosis.[73] Facet joint pain can manifest in a radicular pattern, which is supported by a study that found that the presence of foraminal and central stenosis was positively associated with lumbar medial branch radiofrequency ablation (RFA) outcomes.[74] Irritation of the capsule may also cause reflex spasms of the paraspinous muscles.[69,74,75]

Several experiments conducted by groups of investigators established the pathophysiologic basis for persistent lumbar facet pain. These studies showed that injection of pro-inflammatory and algesic mediators into facet joints resulted in inflammatory changes, leading to sensitization of nociceptors.[76–80] Later work by Chen et al. showed the presence of C and Aδ fibers in the cervical facet joint capsules of goats.[81] C fibers were more prevalent in the dorsolateral aspect of the z-joint capsule, where tendons and muscles attach.

Human Studies

The intervertebral disk and paired facet joints work in concert with changes in any part of the three-joint unit, altering the motion and function of the others. Degenerative disk disease (DDD) has been shown to result in concomitant changes in the facet joints.[82–84] In the reverse scenario, degeneration and motion abnormalities of the facet joints can induce and accelerate intervertebral disk degeneration.[85–87] Multiple studies have examined the relationship between DDD and facet joint OA and concluded that DDD generally precedes facet arthritis[57,88,89] and that facet arthropathy is most pronounced at spinal levels with advanced DDD.[57,88]

The spinal musculature also works collectively with z-joints, controlling movements and stabilizing the vertebral column.[90,91] Paraspinal muscles provide proprioceptive feedback for proper alignment and biomechanics.[91,92] Aging decreases paraspinal muscle mass,[93] which could compromise these functions and contribute to z-joint OA. Patients with chronic LBP seem to have impaired spinal proprioception[94] and a decrease in paraspinal muscle mass.[95] A study by Kalichman demonstrated an association between decreased paraspinal muscle density and the presence of lumbar z-joint OA,[93] while other conditions that can contribute to or cause z-joint OA include degenerative scoliosis[96] and spondylolisthesis.[97]

Several cases of lumbar facetogenic pain secondary to traumatic dislocation from rapid deceleration injuries have been reported, mostly at L5–S1.[60,61,98–102] The purported mechanism of injury in these cases was hyperflexion, rotation, and distraction.[60] Twomey et al. dissected the lumbar spines of 31 patients who died of trauma and noted occult bony fractures in the superior articular process or subchondral bone plate in 35% of subjects and facet capsular or articular cartilage damage in 77% of cases.[103]

For chronic posttraumatic neck pain, the cervical z-joints have been estimated to account for up to 60% of cases.[45] However, trauma is responsible for a relatively small percentage of chronic neck pain, with the prevalence ranging from 13%–42%.[104]

Prevalence

The prevalence of facet joint pain varies greatly in the literature. Among patients with axial spine pain, the proportion of patients with facetogenic pain is higher in the cervical and thoracic regions than in the lumbar region. The problem with estimating the prevalence of facet joint pain is that in the absence of any objective reference standard (e.g. imaging), one must rely on subjective diagnostic procedures such as medial branch blocks or intraarticular injections, which are subject to high technical failure rates (e.g. between 29% and 38% per joint, and from 46% to 64% per

TABLE 31.1 Motions Associated With the Largest Intervertebral Angulation and Strain for the Lumbar Facet Joints

Facet Joint Level	Movement Associated With Maximal IVA	Largest Strain
L1-2	Right bending	Right bending
L2-3	Left bending	Right bending
L3-4	Right bending	Right bending
L4-5	Forward flexion	Forward flexion
L5-S1	Extension	Forward flexion

Modified from Ianuzzi A, Little JS, Chiu JB, et al. Human lumbar facet joint capsule strain I. During the physiological motion. *Spine J.* 2004;4:141–152.

IVA, Intervertebral angle.

procedure in the lumbar spine).[105] There is also a wide variation in the interpretation of blocks (e.g. the threshold of pain relief required to designated a block as positive), with uncontrolled blocks subject to significantly high false positive and false negative rates.[106] Many studies also conflate two different concepts: z-joint arthropathy, which may or may not be painful, and z-joint pain, which may or may not be produced by arthropathy.[107]

The prevalence of LBP stemming from lumbar facet joints is low and is greatly affected by the age of the cohort being tested (i.e. much higher in older individuals) and both the cutoff threshold and number of blocks.[108] In a non-enriched population in which double blocks are employed and cutoff thresholds exceeding 75% are used, the prevalence of lumbar facetogenic pain among individuals with axial LBP is approximately 10%–15%. The prevalence of z-joint-related cervical pain is estimated at 50–55%, increasing to approximately 60% in patients whose neck pain is caused by whiplash. In the thoracic spine, the prevalence is estimated to be between 40% and 50%.[109]

The prevalence of lumbar facetogenic pain is shown in Table 31.2. Earlier studies (1999–2000) by Schwarzer et al.,[55,110,111] Revel et al.,[112] Manchikanti et al.,[113,114,116] and Dreyfuss et al.[115] are not included in the table (Tables 31.2 and 31.3).

Diagnosis

History

Facetogenc pain tends to be insidious and progressive,[127] except for whiplash injuries that follow an acute, traumatic event.[128,129] Young patients with LBP or neck pain are more likely to present with centralized pain that is more indicative of disc disease,[130] while older patients are more likely to have facetogenic pain as the primary pain generator.[9–20] The direct association with age is consistent with the concept that facet pain is a chronic degenerative disorder that coexists with DDD[57] rather than an acute inflammatory process.

Pain Referral Patterns

The distribution and radiation of pain from the facet joints have been derived from relief with LA blocks, pressurization of the facet joints, and stimulation of the medial branches innervating the specific joints. The majority of these studies have failed to demonstrate any reliable pain referral patterns.[131–134]

An important part of the clinical workup is differentiating z-joint pain from other sources of pain.[135,136] A study by DePalma et al.[122] demonstrated that the presence or absence of thigh pain significantly correlated with the source of chronic LBP for varying ages (i.e. thigh pain increased the likelihood of facetogenic vs. discogenic pain in older people). In contrast, the presence of hip/girdle pain or leg pain did not discriminate between discogenic pain, z-joint pain, or sacroiliac joint pain. As previously noted, discogenic pain was more prevalent in younger patients, while z-joint pain was more prevalent in the elderly.[52]

When the existing data are synthesized, certain pain patterns emerged (Figs 31.4–31.6). The joint capsule appears to be more likely to generate pain than the synovium or articular cartilage. A great deal of overlap exists between neighboring facet joints and between discs and facet joints. All lumbar levels are capable of producing groin pain, which is most common at lower levels.[30,72,99,132,137–149] Pain from the upper lumbar facets tends to extend into the flank, hip, and upper lateral aspect of the thigh, whereas pain from the lower lumbar levels is likely to penetrate into the thigh, usually laterally and posteriorly. Infrequently, the L4–5 and L5–S1 facet joints can provoke pain in the lateral part of the calf and rarely in the foot. Patients with osteophytes, synovial cysts, or facet hypertrophy may also have radicular symptoms. Unilateral pain or pain in the paraspinal distribution is more likely to be associated with pain from the facet or sacroiliac joints than with discogenic LBP.[150]

Clinical studies have been conducted in normal volunteers and patients with suspected cervical facet pain to determine pain referral patterns.[151–154] From C2–3, the pain pattern generally extends rostrally to the upper cervical region and suboccipital area. Infrequently, symptoms extend toward the ear or further up the scalp. From C3–4, pain is referred to the upper and middle posterior aspect of the neck, with occasional radiation to the lower occiput. From C4–5, the most common referral pattern is to the lower posterior cervical region, although in many people, it extends to the middle posterior aspect of the neck and suprascapular region. Pain from C5–6 typically radiates to either the suprascapular region or lower part of the neck but sometimes extends to the shoulder joint or midposterior neck region. From C6–7, pain is usually referred to the upper or lower neck area. Pain from the C7–T1 z-joint most frequently extends further down into the midscapular area.

Other joints that can cause cervical pain or headaches are the atlanto-occipital joint and atlanto-axoid joints. Both show highly variable patterns, which may extend over the suboccipital region and the head and face.[155]

Similar work has been done for thoracic z-joints. The pain referral patterns were as follows: pain from the C7–T1 and T1–T2 z-joints typically radiate into the suprascapular region and superior angle of the scapula. Pain extending into the midscapular region may originate from either C7–T1, T1–2, or T2–3, and pain from the T11–12 z-joint generally extends into the paravertebral region around the site of injection around the iliac crest area (Fig. 31.6).[153,156]

Physical Examination

As with historical findings and pain referral patterns, physical examination has limited value in diagnosing facet pain and is more valuable in ruling out other causes of pain. Among the available physical examination findings, the presence of *paraspinous muscle*

TABLE 31.2 Results of Lumbar Facet Joint Pain Prevalence Studies Conducted with Either Placebo-Controlled or Comparative Local Anesthetic Blocks

Author, Year	Patients	Interventions	Results	False Positive Rate and Comments
Manchikanti et al.[117] 2004	397 pts with chronic LBP without neurologic deficits	Pts rec'd MBB with 1% lidocaine. All pts who obtained ≥75% pain relief underwent confirmatory blocks with 0.25% bupivacaine. A (+) response was ≥80% relief lasting longer with bupivacaine.	198 (50%) of pts obtained a (+) response to lidocaine blocks, with 124 reporting definite pain relief with bupivacaine, for a 31% prevalence rate	FP rate, 27%. Mean age, 47 years.
Manchikanti et al. [118] 2007	117 consecutive patients with chronic LBP after lumbar surgical interventions	MBB performed with 1% lidocaine, 0.25% bupivacaine, 0.5 mL. At least 80% of pain relief from block.	Prevalence = 16% (9%–23%)	FP rate = 49% (39%–59%). in patients with failed back surgery syndrome
Manchukonda et al.[119] 2007	303 patients with chronic LBP of at least three months duration following a motor vehicle accident	MBB performed with 1% lidocaine, 0.25% bupivacaine, 0.5 mL. At least 80% pain relief with the ability to perform previously painful movements.	Prevalence = 31% (27%–36%)	FP rate= 27% (22%–32%)
Kavita et al.[120] 2008	Retrospective analysis of 303 patients with chronic lumbar and/or cervical pain divided by age groups (Group I: 18–30 years, II: 31–40 years, III: 41–50 years, IV: 51–60, V: 61–70 years, VI: greater than 70 years old)	Facet joint pain was initially assessed in all patients by diagnostic blocks using 1% lidocaine, followed by 0.25% bupivacaine if the responses to lidocaine were positive on two separate occasions, usually separated by three to four weeks. A positive response was defined as: 1) at least an 80% reduction of pain, 2) the ability to perform previously painful movements (as assessed using a verbal numeric pain rating scale), 3) pain relief from a block lasting at least 2 h when lidocaine was used and at least 3 h when bupivacaine was used.	The prevalence of facet joint involvement in lumbar spinal pain ranged from 18% (in Group II: 31-40 years) to 44% (in Group IV: 51-60 years), with significant differences noted when Group II and Group III were compared to other groups, and with higher rates in Group V.	Overall FP rate 45% (36%–53%) Group I: 40% (20%–60%) Group II: 50% (26%–74%) Group III: 45% (30%–60%) in Group IV: 30% (12%–47%) Group V: 64% (43%–84%) Group VI: 43% (16%–69%)
Manchikanti et al.[121] 2010	181 patients with chronic low back pain	MBB performed with 1% lidocaine, 0.25% bupivacaine, 0.5 mL. Compared, 50% pain relief with 80% pain relief.	50% pain relief Prevalence = 61% (53%–81%) 80% pain relief Prevalence = 31% (26%–35%)	50% pain relief FP rate = 17% (10%–24%) 80% pain relief FP rate = 42% (35%–50%)
DePalma et al.[122] 2011	Retrospective evaluation of 156 patients with CLBP were assessed for the source of chronic LBP (discogenic pain, facet joint pain, and sacroiliac joint pain)	MBB performed with 1% lidocaine, 0.5% bupivacaine. Concordant relief for 2 h for lidocaine and 8 h for bupivacaine with 75% pain relief as the criterion standard	Prevalence = 31%	Study evaluated various structures implicated in LBP with controlled diagnostic blocks

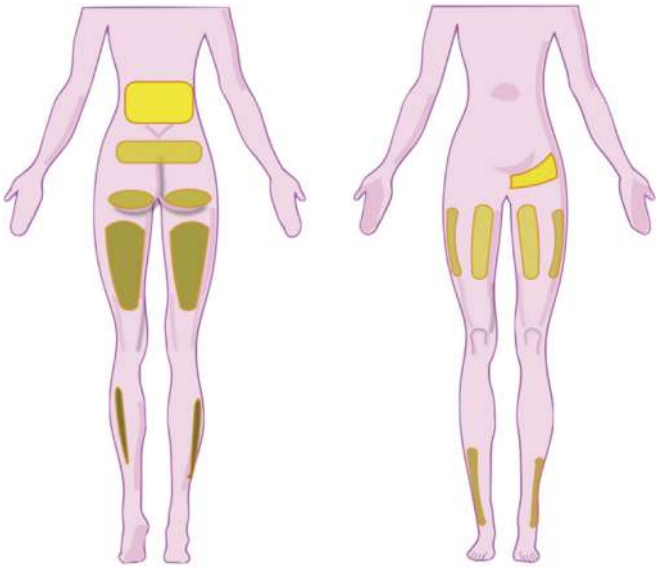
The false positive (FP) rate, if not mentioned, was determined by dividing the number of patients who obtained pain relief with the lidocaine screening block but not with the confirmatory block by the total number of blocks. *LA*, Local anesthetic; *LBP*, low back pain; *MBB*, medial branch block; *pts*, patients; *rec'd*, received.

The prevalence of lumbar facetogenic pain is shown in Table 31.2. Earlier studies (1999-2000) by Shwarber et al.,[55,110,111] Revel et al.,[112] Manchikanti et al.,[113,114,116] and Dreyfuss et al.[115] are not included in the table.

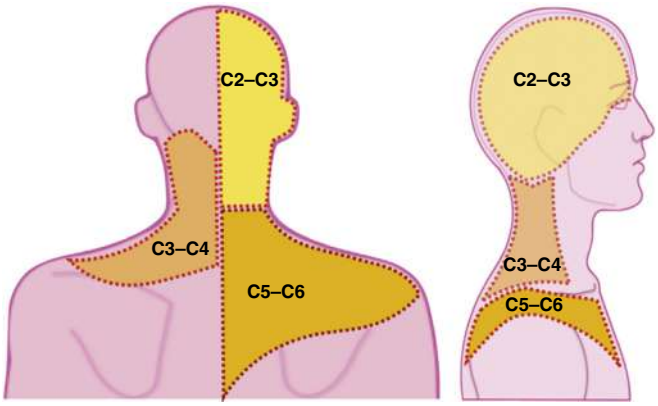
TABLE 31.3 Results of Cervical and Thoracic Zygapophyseal Joint Pain Prevalence Studies Conducted With Either Placebo-Controlled or Comparative Local Anesthetic Blocks

Author, Year	Patients	Interventions	Results	False Positive Rate and Comments
Barnsley et al.[41,47] 1993	47 pts with chronic neck pain >3 months after MVA	Pts rec'd cervical MBB with 0.5 mL of either 2% lidocaine or 0.5% bupivacaine. Pts with positive block rec'd other agent. A (+) response required longer pain relief with bupivacaine.	27 pts had longer relief with bupivacaine than with lidocaine, for a 60% prevalence rate.	13 pts (27%) had a (+) response to both LAs but in excess of the expected duration. Average age, 41 years. Female-male ratio, 1:1. All but three pts involved in litigation.
Barnsley et al.[123] 1995	50 pts with chronic neck pain of >3 months duration after a whiplash injury from MVC	Pts rec'd cervical MBB with 0.5 mL of either 2% lidocaine or 0.5% bupivacaine at random. Pts with a (+) block rec'd the complementary anesthetic. A (+) response required longer pain relief with bupivacaine.	27 pts who completed the study met the criteria for a (+) painful joint, for a 54% prevalence rate.	Ten pts (20%) had longer pain relief with lidocaine than with bupivacaine or no pain relief with repeated blocks. Average age, 41 years. Female-male ratio, 1.5:1. C2-3 and C5-6 most frequently affected levels.
Lord et al.[51] 1996	68 pts with chronic neck pain of >3 months duration after a whiplash injury from MVA	Pts rec'd diagnostic C2-3 blocks to rule out those with third occipital headache. Placebo-controlled cervical facet blocks below C2-3 were done with 0.5 mL of either 2% lidocaine or 0.5% bupivacaine. If (–), other levels were then attempted. If (+), pts rec'd either NS or other LA at random and then had a third block with the remaining agent.	31 of 52 pts (60%) who completed the study had cervical facet pain at C2-3 or below, for a 60% prevalence rate. Among pts with HA as the dominant Sx, 50% prevalence of C2-3 facet joint pain. In pts without C2-3 facet pain, the prevalence of lower cervical facet pain was 49%.	Average age, 41 years. Female-male ratio, 2:1. C2-3 and C5-6 most commonly affected levels.
Manchikanti et al.[124] 2002	46 pts with chronic thoracic pain (>6 months) without neurologic Sxs	Pts rec'd MBB with 1% lidocaine followed by confirmatory blocks with 0.5% bupivacaine. A (+) response was ≥80% concordant pain relief.	22 of 36 pts with (+) lidocaine blocks had longer relief with confirmatory bupivacaine blocks, for a 48% prevalence rate.	FP rate, 58%. Average age, 46 years.
Manchikanti et al.[125] 2002	106 pts with chronic neck pain with or without HA or upper extremity pain	Pts rec'd diagnostic blocks with 0.5 mL of 1% lidocaine followed by 0.5 mL of 0.25% bupivacaine two weeks apart.	64 of 81 pts with (+) lidocaine blocks had longer relief with confirmatory bupivacaine blocks, for a 60% prevalence rate	40% FP rate. Mean age, 43 years. Female-male ratio, 2:1. 15% of pts had previous neck surgery.
Manchikanti et al.[117] 2004	500 pts with chronic neck, thoracic, and/or LBP without neurologic Sxs. 255 pts had cervical Sxs, and 72 pts had thoracic Sxs	Pts rec'd MBB with 1% lidocaine followed by confirmatory blocks with 0.25% bupivacaine. A (+) response was ≥80% relief lasting longer with bupivacaine. Minimum of two levels blocked based on pain patterns.	55% prevalence rate of cervical facet joints in pts with cervical spine pain. 42% prevalence rate of thoracic facet joints in pts with thoracic pain.	FP rate of 63% for cervical and 55% for thoracic MBB. Average age, 47 years. Female-male ratio, 2:1 for both cervical and thoracic.
Manchukondet al.[119] 2007	251 patients with chronic neck pain of at least six monthsduration. Non-specific with no radicular component	1% lidocaine 0.25% bupivacaine 0.5 mL volume	Pain relief ≥80% with the ability to perform previously painful movements	Prevalence = 39% (32%–45%) FP rate= 45% (37%–52%)
Yin and Bogduk[126] 2008	84 patients with chronic neck pain of at least three months duration	4% lidocaine 0.75% bupivacaine 0.5 mL	100% pain relief with duration of response concordant with the anesthetic used	

HA, headache; *MVC*, motor vehicle collision; *MVA*, motor vehicle accident; Sxs, symptoms.



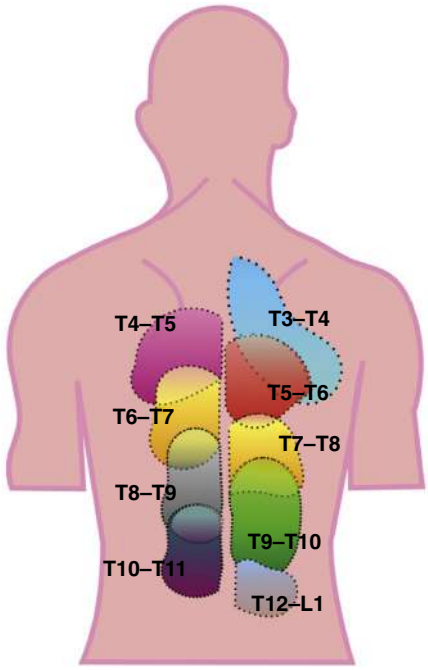
• **Figure 31.4** Pain referral patterns from the lumbar facet joints. The most common referral patterns extend from the darkest (low back) to the lightest regions (flank and foot) in descending order. The following key is listed in order of affected frequency (i.e. low back to foot). The facet levels next to each location represent the zygapophyseal joints most associated with pain in each region. Low back: L5-S1, L4-5, L3-4; buttock: L5-S1, L4-5, L3-4; lateral thigh area: L5-S1, L4-5, L3-4, L2-3; posterior thigh area: L5-S1, L4-5, L3-4; greater trochanter: L5-S1, L4-5, L3-4, L2-3; groin: L5-S1, L4-5, L3-4, L2-3, L1-2; anterior thigh area: L5-S1, L4-5, L3-4; lateral lower leg area: L5-S1, L4-5, L3-4; upper back area: L3-4, L2-3, L1-2; flank: L1-2, L2-3; foot: L5-S1, L4-5. (Adapted from Cohen, SP, Raja SN. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial facet joint pain. *Anesthesiology*. 2007;106:591–614.)



• **Figure 31.5** Pain referral patterns from the cervical facet joints. (Adapted from Bogduk N, Marsland A. Cervical zygapophysial joints are a source of neck pain. *Spine*. 1988;13:615.)

tenderness on palpation is probably the only sign weakly indicative of facetogenic pain.[157,158] This finding is likely because of sensitized musculature rather than actual strain on the facet joints.

Despite the limited value of physical examination in diagnosing facet pain, many research studies and clinicians still rely on provocative maneuvers to select patients for facet interventions. A study showed that patients who responded to intraarticular injections were more likely to have back pain associated with groin or thigh pain, paraspinal tenderness, and reproduction of pain with



• **Figure 31.6** Pain referral patterns from the thoracic facet joints. (Adapted from Dreyfuss P, Tibiletti C, Dreyer SJ. Thoracic zygapophysial joint pain patterns. A study in normal volunteers. *Spine*. 1994;19:809.)

extension rotation maneuvers.[145] Pain radiating below the knee was a negative predictor.

Larger and more methodologically sound studies have failed to validate "lumbar facet syndrome" or the provocative maneuver commonly known as "facet loading." Prospective studies of patients with chronic LBP could not correlate any historical or physical findings associated with a positive response to facet injections.[145,159] In both studies, only a small percentage (10% and 15%, respectively) of patients responded to diagnostic blocks. A randomized, placebo-controlled study of 80 patients with chronic LBP by Revel et al. found seven factors to be associated with response to facet joint anesthesia: age older than 65 years and pain not exacerbated by coughing, not worsened by hyperextension, not worsened by forward flexion, not worsened when rising from forward flexion, not worsened by extension rotation maneuvers, and well relieved by recumbency.[112] However, subsequent investigations failed to corroborate these findings.[160]

Very few studies have investigated the history and physical findings most consistent with cervical and thoracic facet pain. One study found that a blinded therapist specializing in manipulation could correctly diagnose symptomatic cervical facet joint pain in patients with positive diagnostic cervical MBBs through the perceived passive displacement of the joint and its resistance to displacement.[161] However, a subsequent study conducted using controlled blocks as the "gold standard" for cervical z-joint pain found that although manual examination had a sensitivity of 88%, low specificity (39%) precluded its use as a valid diagnostic tool.[162] The majority of cervical facet prevalence studies have been conducted on whiplash victims, thereby making it difficult to draw conclusions in non-trauma patients. A Delphi study from an expert panel identified 12 indicators of lumbar joint pain. Those that reached the highest levels of consensus were a positive response to facet joint injection, localized unilateral LBP, positive medial branch block, paraspinal tenderness, absence of radicular

features, pain eased by flexion, and pain, if referred, located above the knee.[163] A study by Laslett found seven characteristics suitable for selecting patients for interventions involving the lumbar z-joints: 1) age 50 years or greater, 2) pain relieved when walking, 3) pain improved by sitting, 4) paraspinal pain predominance, 5) Modified Somatic Perception Questionnaire score exceeding 13, 6) positive extension rotation test, and 7) absence of centralization during repeated movement testing.[53] Recently, a meta-analysis by Usunier et al. identified four clinical tests that predicted cervical facet joint pain: passive intersegmental motion testing; mechanical sensitivity; pain consistent with cervical zygapophyseal joint referral patterns; and, based on a single study, a positive extension rotation test.[164] However, the sensitivity and specificity of these tests were poor.

Radiologic Findings

The prevalence of facet joint disease observed on radiologic imaging is dependent on the age of patients, presence of symptoms, imaging modality, and threshold used for designating an examination as "abnormal." In LBP patients, the prevalence of degenerative facet disease on computed tomography (CT) ranges from 40% in some studies[165] to 85% in others.[166,167] Studies comparing the sensitivity and specificity of MRI and CT in detecting facet degenerative changes are not uniform (Table 31.4).[88,169,170] In a study of 14 patients with DDD, those younger than 40 years showed minimal osteoarthritic changes of the lumbar facets.[88] The prevalence of facet pathology increased significantly in patients older than 60 years. In asymptomatic volunteers, the incidence of lumbar facet degeneration ranges from 8% to 14%.[168,171,172]

The use of radiologic imaging as a predictor of response to diagnostic facet blocks has been conflicting. Although some studies have found a positive association between CT, MRI, and other imaging modalities and response to facet blocks,[165,173] an equal number have not.[54,146,166,133,174]

Recent studies have focused on newer imaging modalities.[175,176,177] A study by Rosen showed a positive correlation between the severity of degenerative disk and facet disease on PET/MRI using an 18-F FDG radiotracer.[178] However, Lehman and Diehm more recently demonstrated poor concordance between peri-facet joint signal changes and facet joint pain.[179] In a study by Yolcu and Lehman comparing hybrid imaging techniques (PET/CT, PET/MRI, and single-photon emission computed tomography [SPECT]/CT) to evaluate back and neck pain because of suspected z-joint arthropathy, the authors concluded that while they are promising, increased radiation exposure and higher costs must be considered.[180]

In summary, the literature does not support the routine use of radiologic imaging as a means of diagnosing facet pain. The lack of an association between imaging findings and facet joint pain is consistent with other musculoskeletal pain disorders such as knee and hip osteoarthritis.[181,182,183]

Diagnostic Blocks

The poor correlation between historical, radiologic, and physical examination findings and zygapophyseal pain has led to widespread acceptance of the use of diagnostic blocks to confirm facet joints as primary pain generators.[184] Although MBB and intraarticular injections are widely touted to be equally effective diagnostic tools,[185] the evidence for this claim is based on two studies, neither of which used a crossover design, controlled blocks, or prescreened patients for z-joint pain.[148,186] Several factors undermine the diagnostic validity of MBB. In a cadaveric study done in the late 1930s, Kellegren showed that injection of 0.5 mL of fluid spread into an area encompassing 6 cm^2 of tissue.[187] Cohen and colleagues demonstrated that reduction in LA volume in cervical MBBs from 0.5 to 0.25 mL decreased aberrant spread to other potential pain generators, including spread to the intervertebral foramen, by over 50%.[188] Because of the short distance between branches of the dorsal rami, even low-volume medial branch blocks are likely to block the lateral and intermediate branches. Since these nerves supply afferent innervation to multiple potential pain-generating structures, including the paraspinal muscles, ligaments, sacroiliac joints, and skin, MBB can relieve pain even in the presence of non-pain-generating z-joints. False positive rates have been reported to be as high as 63% in the cervical region, 53% in the thoracic region, and 27% in the lumbar facet region.[117] However, the higher prevalence (true positive) rates in the neck and midback should theoretically result in a lower false-positive rate. False negative responses are also a concern as they can limit access to care and result from intravascular uptake of the LA, procedure-related pain, and failure of patients to distinguish between pain from the procedure and their baseline pain. Considering the low sensitivity of aspiration and intermittent fluoroscopy, some advocate using "real-time" fluoroscopy to detect intravascular uptake during MBB.[189]

Although intraarticular facet injections may be more theoretically accurate in diagnosing facet pain, these blocks can be technically challenging and fraught with limitations. Injection of >2 mL of fluid can rupture the joint capsule and lead to extravasation of LA onto other pain-generating structures, leading to false positive blocks. Depending on the point of extravasation, these structures can include the epidural space, intervertebral foramen, ligamentum flavum, and paraspinal musculature.[68,149]

Medial Branch Block Versus Intraarticular Injection

The argument supporting a prognostic procedure that targets the nerves rather than the joints themselves is supported by a multicenter case-control study demonstrating better radiofrequency ablation outcomes in patients who undergo medial branch blocks rather than intraarticular injections.[190]

A study by Ackerman and Ahmad randomized 46 patients with axial LBP and a positive SPECT scan to receive either intraarticular injections or MBB using 0.7 mL of LA and steroid. Twelve weeks after treatment, 61% of the intraarticular injection group experienced a positive outcome, which favorably compared with 26% in the MBB group.[191] It is difficult to draw conclusions based on these comparative studies because of the multitude of design flaws. The most prominent ones are the lack of a definitive diagnosis in the study populations and that only one study[186] evaluated immediate post-procedure pain relief. Studies investigating the prevalence and false positive rates in chronic LBP patients (Table 31.2) have generally found comparable diagnostic values for MBB and intraarticular injection. None of the three placebo-controlled studies evaluating the outcome of lumbar RF denervation after intraarticular injections to "confirm" the presence of facetogenic pain demonstrated definitively positive outcomes.[192,–194] In contrast, most studies that screened patients with lumbar MBB demonstrated a primary positive outcome.[195] In a prospective, randomized study comparing lumbar facet cryodenervation success rates between patients who underwent medial branch and pericapsular lumbar facet screening blocks, Birkenmaier and associates[196] found superior outcomes up to six months after the procedure in the MBB group. However, the excessive volumes used during both diagnostic procedures, the absence of

TABLE 31.4 Prospective Clinical Trials Evaluating Intraarticular Steroid Injections for Lumbar and Cervical Facet Joint Pain

Authors, Year, Methodology Score	Patients and Interventions	Results	Comments
Carette et al.[220] 1991; MQ score = five	97 pts with chronic LBP who reported immediate relief after injections of 2 mL of steroid and saline (n = 49) or saline (n = 48) into the L4-5 and L5-S1 lumbar z-joints.	42% of pts who received steroids and 33% who rec'd placebo reported marked improvement for up to three months (not significant). At six months, the steroid group reported less pain and disability. Only 22% of pts in the steroid group and 10% in the placebo group had improvement through six months.	Differences between groups at six months reduced when co-interventions were taken into account. NS is known to provide pain relief greater than that expected from a placebo.
Marks et al.[149] 1992; MQ score = three	86 pts with chronic LBP were randomized to receive either 1.5 mL of steroid and LA MBB or intraarticular injections (2 mL at the lowest level).	Pts who rec'd facet joint injections had better pain relief than did those who underwent MBB at all follow ups, but this was significant only at one month.	Flaws include no true control group, failure to identify pts based on diagnostic injections, no monitoring of co-interventions, and lack of a blinded observer.
Barnsley et al.[221] 1994; MQ score = five	41 pts with chronic neck pain following MVA were randomized and received an injection of either 1 mL of 0.5% bupivacaine or 5.7 mg of betamethasone into painful cervical z-joints diagnosed by comparative LA MBB.	Less than half the pts reported relief for more than one week, and fewer than one in five reported relief for more than one month. The median time to return of 50% of the preprocedure pain was three days in the steroid group and 3.5 days in the LA group.	All pts had neck pain following a whiplash injury. Some pts with long-lasting benefit in both groups.
Fuchs et al.[218] 2005; MQ score = one	60 pts with chronic LBP were randomized to either 1 mL of HA or steroid into the three lowest facet joints at weekly intervals for six weeks.	Pts who rec'd HA injections experienced a 40% decrease in pain scores vs. a 56% reduction in those who rec'd steroid (not significant). The greatest pain reduction was observed after three months in the HA group and after one week in the steroid group.	Inclusion criteria included at least moderate facet degeneration on radiologic imaging. Flaws include lack of a control group, failure to identify pts based on diagnostic injections, no monitoring of co-interventions, and multiple injections.
Pneumaticos et al.[222] 2006; MQ score = three	47 pts with chronic LBP and radiologic evidence of lumbar z-joint abnormalities were randomized in a 2:1 ratio to undergo intraarticular LA and steroid injections (3 mL) based on SPECT scans or physical examination.	One month after injection, 87% of pts with (+) SPECT had significant pain improvement vs. 12.5% of pts with (–) SPECT and 31% of pts who underwent injections based on physical examination.	Differences remained significant at three months but not six months. No functional assessment was done. The use of SPECT was cost effective.
Kennedy et al.[225] 2018; MQ score = three	28 subjects with confirmed z-joint pain via dual comparative medial branch blocks were randomized to receive either intraarticular corticosteroid (triamcinolone 20 mg) or saline via fluoroscopic guidance.	There was no statistically significant difference in the need for radiofrequency ablation between groups, with 75% of the saline group and 91% of the corticosteroid group receiving neurotomy. No difference was observed in the mean time to radiofrequency neurotomy between saline (6.1 weeks) and corticosteroid (6.5 weeks) groups.	Corticosteroid injections into the lumbar z-joints were not effective in reducing the need for radiofrequency neurotomy in those with z-joint pain confirmed by medial branch blocks.
Cohen, et al.[105]2018; MQ score four	229 patients were randomized in a 2:2:1 ratio to receive intraarticular facet injections with LA and steroid, medial branch blocks with LA and steroid, or saline.	Mean reduction in average numeric rating scale pain score at one month was 0.7 ± 1.6 in the intraarticular group, 0.7 ± 1.8 in the medial branch block group, and 0.7 ± 1.5 in the placebo group; P = 0.993. The proportion of patients with positive blocks was higher in the intraarticular (54%) and medial branch (55%) groups than in the placebo group (30%; P = 0.01). Radiofrequency ablation was performed on 135 patients (45, 48, and 42 patients from the intraarticular, medial branch, and saline groups, respectively). The mean reduction in average pain score at three months was 1.8 ± 2.3 in the intraarticular, 1.8 ± 2.4 in the medial branch, and 0.7 ± 1.5 in the control group (P = 0.025). At three months, the proportions of positive responders in the intraarticular, medial branch block, and placebo groups were 51%, 56%, and 24%, respectively (P = 0.005).	This study establishes that facet blocks are not therapeutic. The higher responder rates in the treatment groups suggest that facet blocks might provide prognostic value before radiofrequency ablation.

The methodologic quality (MQ) score is based on the five point Jadad scale.[223] A score of three or higher indicates high methodologic quality.

HA, Hyaluronic acid; *LA*, local anesthesia; *LBP*, low back pain; *MBB*, medial branch block; *MVA*, motor vehicle accident; *NS*, normal saline; *pts*, patients; *rec'd*, received; *SPECT*, single-photon emission computed tomography; *z-joint*, zygapophyseal (facet) joint.

controlled blocks, and the lack of proven validity for pericapsular injections detract from the authors' conclusions.

The most recent randomized study published in 2018 by Cohen et al.[105] compared the therapeutic and prognostic value of intraarticular blocks and medial branch blocks performed with bupivacaine and steroids and sham injections. Among patients in the intraarticular and medial branch block groups who experienced a positive block but failed to derive long-term (≥3 months) relief, radiofrequency ablation was performed. In the sham group, radiofrequency ablation was performed in all non-responders. The authors determined that the strongest factor associated with a positive radiofrequency ablation outcome was a positive outcome from a true diagnostic block, with medial branch and intraarticular injections having comparable prognostic value. The difference in radiofrequency ablation outcomes between the treatment groups and the control group was small but statistically and clinically meaningful. Finally, the authors found no meaningful benefit at one month or subsequent time points between either of the true injections and the placebo.

Intraarticular injections can be technically challenging, especially in the steep, frontally oriented thoracic facet joints.[197] In addition, MBB involves anesthetization of the nerves to be lesioned and hence may serve as a "dry run" before definitive treatment, similar to performing a selective nerve root block before surgical decompression. Multiple guidelines, including those by the 14 participating federal and international organizations,[185] have endorsed lumbar medial branch blocks but not intraarticular injections based on face validity,[107] target-specificity,[24] and construct validity,[198] as a selection tool for medial branch neurotomy.[150] Given the lack of evidence for intraarticular injections as a superior diagnostic tool and the technical ease of performing MBB, MBB is recommended as the prognostic tool of choice for subsequent medial branch denervation.

False Positive Blocks

Numerous studies have found a high false positive rate for diagnostic facet blocks that appear unaffected by the type of block used (i.e. intraarticular or MBB). Published rates have ranged from 25% – 40% in the lumbar spine,[114,117,185,198] 58% in the thoracic spine,[124] and 27%–63% in the cervical spine.[47,117,125,161,199] A study showed high specificity and marginal sensitivity of serial local anesthetic cervical MBBs with lidocaine and bupivacaine.[200] Although high specificity will result in a low false positive rate, the low sensitivity predisposes patients to false negative diagnoses, thereby reducing access to care.

Reasons for false positive facet blocks are multifactorial and include a placebo response (18%–32%) to diagnostic interventions, use of sedation, liberal use of superficial LA, and spread of injectate to other pain-generating structures.[201] The International Facet Joint Guidelines Committee,[185] the American Society of Anesthesiologists,[202] and the Spine Intervention Society[203] all recommend against the routine use of sedation. Dreyfuss et al. used postprocedural CT scans following 120 fluoroscopically guided lumbar MBBs to assess the specificity and spread of contrast material.[31] Two target points were chosen: one at the superomedial border of the transverse process and a second lower site midway between the upper border of the transverse process and the MAL. In 16% of injections, contrast material was noted to spread into the intervertebral foramen or epidural space, which was more common at the upper target point. In all cases, distal spread into the cleavage plane between the multifidus and longissimus muscles was noted. The injectate volume (0.5 mL) bathed the target in every case, leading the authors to conclude that lower volumes may be adequate. In a study of 24 patients undergoing cervical MBB, Cohen et al. investigated the spread of LA (0.5 mL versus 0.25 mL) mixed with contrast agent.[188] MBBs were performed in either the prone or lateral position. CT scans were conducted following MBBs to assess aberrant spread. Blocks performed in the 0.25 mL group resulted in aberrant spread to untargeted adjacent levels and into the intervertebral foramina less than half as often as those in the 0.5 group. There were six "missed" medial branches in the 86 blocks performed, which were evenly distributed between the groups. These findings indicate that lower volumes may enhance specificity without affecting sensitivity.

To reduce the amount of superficial anesthetic used for MBB, Stojanovic et al. introduced a single-needle technique whereby multiple medial branches are blocked via a single skin entry point.[204] In a prospective crossover study comparing the single-needle and conventional multiple-needle techniques, the authors found that the single-needle technique required significantly less superficial LA, resulted in less procedure-related pain, and was faster to perform than the multiple-needle approach.[205] With regard to the final needle position, spread of contrast material, and postprocedural pain relief, no differences were noted between the two techniques.

False Negative Blocks

Similar to false positive blocks, false negative blocks may result from many factors. The prevalence of false negative blocks can never be known for certain in the absence of a pathognomonic reference standard, but in a retrospective study by Derby et al.,[206] the false negative rate (determined by a subsequent positive block using 70% pain relief as the cutoff) was 47% in individuals who obtained <50% relief and 47.1% in those who experienced 50%–69% relief, with 75% of these patients achieving ≥50% pain relief after radiofrequency ablation. One study estimated the incidence of false negative lumbar MBBs attributable to non-medial branch aberrant innervation to be approximately 11%.[150] A person whose facet joints are innervated by nerves other than the medial branches can theoretically respond to intraarticular blocks but fail to derive relief with technically successful medial branch neurotomy. Venous uptake of LA was reported to occur in 8% of lumbar facet blocks in one study,[31] and 33% in another.[149] In one of these studies, even after the needle was repositioned following vascular uptake, the injection of LA failed to prevent pain from capsular distention in 50% of subjects.[149] This has led some purists to advocate aborting medial branch blocks when intravenous uptake is detected.[149] In a study involving more than 1400 lumbar MBBs in 456 patients, Lee et al. found a 6.1% rate of uptake of LA, which was detected in 34% of the patients by aspiration and in 59% by spot fluoroscopy.[207] Digital subtraction angiography is considered the reference standard for detecting intravascular uptake during medial branch blocks. One large study found a 19% incidence of vascular uptake with digital subtraction, compared with 11% using real-time contrast administration and 6.7% with aspiration. One of the biggest causes of false negative blocks is the failure of patients to properly distinguish procedure-related pain from their index pain, which underscores the need for proper patient education (Box 31.1).

How Many Blocks Should Be Performed Before Radiofrequency Denervation?

Many experts and organizations advocate performing multiple diagnostic blocks to reduce the high false positive rate.[208,209,210] There are two problems with this argument. First, reducing the

• BOX 31.1 Interventions That May Reduce the Incidence of False Positive and False Negative Lumbar Facet Blocks

1. Perform placebo-controlled blocks or, if not possible, comparative local anesthetic blocks.
2. Aim for a lower target point on the transverse process.
3. Reduce the injectate volume to 0.5 mL or less.
4. Be judicious with the use of superficial anesthesia.
5. Consider a single-needle approach.
6. Consider using guidance with computed tomography when doing intraarticular injections in patients with severe spondylosis.
7. Avoid the use of sedation or opioids.
8. Use dye to identify vascular uptake and confirm spread to neural targets.
9. Use small needles to reduce procedure-related pain.

false positive rate is important when trying to establish "efficacy" but may be counterproductive when one's objective is "effectiveness," which seeks to maximize outcomes under real-life conditions. To illustrate this point, many controlled studies evaluating RF denervation have screened hundreds of patients to enroll several dozen subjects. Although the results of a positive study are cited many times, the ultimate outcomes of hundreds of patients excluded from participation remain unknown. Second, many of these "false positive" blocks may include "false negatives."[148,211–213] Although performing multiple blocks will reduce the false positive rate, it will inexorably increase the false negative rate, which reduces access to care. Eliminating placebo responders may not only be impossible but also impractical since the benefits experienced from a positive "sham" intervention are indistinguishable from those experienced with a "true" intervention.[214]

In an attempt to determine the ideal number of diagnostic blocks under "real-life" circumstances, Cohen and colleagues performed a randomized, comparative cost effectiveness study in which 151 patients were allocated in an equal ratio to receive lumbar facet RF denervation without MBB, after a positive response to one MBB performed with bupivacaine, or only after a concordant response to comparative blocks performed in random order with lidocaine and bupivacaine.[215] Predictably, a higher RF success rate was found in the double-block group, which is consistent with the use of this treatment paradigm in clinical efficacy trials. However, the overall number of patients who experienced a successful outcome at three months was significantly higher in the zero-block group (n = 17) than in the single- (n = 8) and double-block (n = 11) groups. Moreover, the cost per effective treatment and the overall costs in the zero-block group were less than half of those in the other two groups. The results of this study are bolstered by theoretical computations that have determined that "double blocks" are not cost effective at current reimbursement rates.[216]

Similar comparative effectiveness studies have not been performed for cervical facet joint pain.[217] However, because the relative reimbursement rates between diagnostic blocks and RF denervation are comparable in the neck and facetogenic pain accounts for a higher proportion of chronic neck pain than chronic LBP, these results are likely to be reliably extrapolated to cervical facet joint RF denervation. The use of a single block is advocated by the International Lumbar Facet Guidelines Committee.[185] These guidelines also advocate a personalized approach, such that an older person with paraspinal tenderness and severe facet joint degeneration on anticoagulation could receive RF ablation without a screening block. In contrast, double blocks should be considered in a clinical trial or a young athlete with a diffuse pain phenotype.

Intraarticular Steroid Injections: Are They Diagnostic, Therapeutic, Or Both?

There is controversy regarding the use of intraarticular LA and steroid injections to diagnose and treat facet pain.[218] In uncontrolled studies, success rates in individuals undergoing intraarticular steroid injections range from 18%–63%, with most of these studies being conducted in patients who did not undergo diagnostic screening blocks.[105,143,148] Unlike medial branch blocks, which may result in false positive diagnoses by blocking non-medial branch nerves, and false negative diagnoses in patients with non-medial branch innervation, intraarticular injections technically meet the criteria for a "diagnostic" intervention. However, the high technical failure rate (which can lead to false positives and false negatives) and significant procedure-related pain in technically challenging blocks (which can lead to false negatives) undermine the diagnostic value of intraarticular injections.[185]

The results of controlled trials evaluating the diagnostic and therapeutic value of intraarticular injections have been mostly negative (Table 31.4).[105,144,186,218–223] A single-blind, triple crossover study[224] that compared lumbar intraarticular placebo injections, sham (needle placement outside of the joints without injection) procedures, and verum injections found equivalence between true and placebo injections and partial equivalence between verum and sham procedures, with a high placebo response. The authors concluded that a single intraarticular lumbar facet injection had little diagnostic value. In a large study, Lilius et al.[219] found no significant differences in the outcomes of 109 patients who received large-volume (8 mm) LA and steroid injected into two lumbar facet joints, the same mixture administered around the joints, or physiologic saline. In another study comparing intraarticular steroid and saline in 97 patients with chronic LBP, Carette et al. found a statistically significant benefit only at the six month mark in the steroid group.[220] Barnsley et al. randomized 41 patients with chronic neck pain following an MVA to receive 1 mL of either intraarticular bupivacaine or betamethasone under double blind conditions.[221] The median time to return of 50% of the patient's pre-injection pain was three days in the steroid group and 3.5 days in the LA group, with less than half of the patients reporting pain relief lasting longer than one week. All patients in this study were prescreened for cervical z-joint pain via comparative MBB.

Basic science studies demonstrating inflammatory mediators around degenerated facet joints form a theoretical underpinning for the potential benefit of intraarticular steroids.[16,17] There is some evidence to support this assertion, as evidenced by several prospective and observational studies that evaluated low to intermediate volume (1–3 mL) LA and steroid intraarticular lumbar facet joint injections performed in more than 160 patients with axial LBP.[176,191,222,223] In these studies, patients with positive SPECT findings experienced better pain relief (>75% success rate) than those with no SPECT findings (<40% success rate) up to three months after injection. In two earlier studies that monitored patients for six months post-injection, the beneficial effect wore off after three months.[218,222] However, two recent high quality studies have also questioned the therapeutic efficacy of intraarticular joint injections. A double blind, placebo-controlled study by Kennedy et al.[225] used comparative medial branch blocks as the diagnostic

criterion to enroll 28 patients with lumbar facetogenic pain. The authors found that corticosteroids injected into the z-joints were ineffective in reducing the need for radiofrequency neurotomy, although their primary endpoint changed. A two phase, placebo-controlled trial by Cohen et al.[105] (FACTS study) randomized 229 patients in a 2:2:1 ratio to receive intraarticular lumbar facet injections, medial branch blocks, or a placebo. The main conclusions of this study are as follows.

- The failure rate of intraarticular injections is substantial, 29% per technical joint.
- The strongest factor associated with a positive RFA outcome was a positive diagnostic block.
- Medial branch blocks and intraarticular injections had comparable prognostic value for radiofrequency ablation, with both being superior to placebo injections.
- Intraarticular facet injections are not therapeutic in most people.

Diagnostic/Prognostic Blocks

Diagnostic blocks involve technical acumen and variables such as an understanding of anatomy and the literature, communication skills (i.e. explaining to patients to engage in normal activities and discount procedure-related pain), and interpretation of what is often conflicting information. Diagnostic blocks help practitioners choose patients who are likely to benefit from radiofrequency denervation. The basic problem is that they rely on subjective measures over short periods. Although blocks may refine the selection and improve outcomes, they rarely provide a definitive diagnosis.

Treatment

Conservative Treatment and Pharmacotherapy

A multimodal approach for the treatment of facetogenic pain is essential. Although many patients seen in interventional pain medicine clinics will receive a procedural approach to therapy, there is value in conservative therapy, medical management, and, when indicated, psychotherapy. Pharmacotherapy, psychotherapy, and non-interventional integrative treatments of spinal pain have been investigated, but no study has evaluated these alternatives specifically in patients with facet pain. Currently, the international facet joint guidelines recommend at least three months of conservative care before proceeding with procedural interventions.[185]

Regenerative Treatments

In the past 10 years, numerous studies have been performed to evaluate treatment options in which the body's own healing armamentarium could be used to treat degenerative pathologies such as facetogenic spinal pain. These treatments aim to potentiate and assist the normal healing process of the body in damaged tissues. Many substances have been studied to determine whether the normal course of tissue degeneration can be altered.

- Platelet-rich plasma (PRP): PRP is a concentrate of whole blood centrifuged to obtain plasma rich in growth factors and platelets acquired from autologous blood. The basis for PRP is that platelets are essential in anabolic healing processes.[226,227,228] Although several studies have demonstrated benefit from intraarticular PRP, large, randomized controlled studies are lacking.[229–231]
- Mesenchymal signaling cells: Mesenchymal signaling cells (MSCs) are cells capable of proliferation and differentiation into cells that promote tissue regeneration.[232] They are present in several tissues (blood, adipose tissue, and muscle) and possess both immunomodulatory and anti-inflammatory effects.[233] They can be harvested from bone marrow or adipose tissue. No study has evaluated the injection of MSCs into facet joints, although promising results have been obtained for other synovial joints.[234]

Guidelines by the American Society of Interventional Pain Physicians reported that the level of evidence for regenerative treatments for lumbar facet joint pain was IV out of V, based on mostly low quality studies.[235] The authors concluded that regenerative therapies should be provided to patients as a stand-alone treatment or in conjunction with other therapies, following diagnostic evidence of pathology likely to respond to therapy. Recent studies have also evaluated biologic replacements for degenerated and painful facet joints.[236] Several scaffold-based approaches are currently being investigated, with some clinically available for the knee and other large joints. New 3-D printers are capable of producing shape-specific cartilage to replace facet joint cartilage.[237] Despite these promising strategies, the evidence supporting biologic and surgical replacement therapies are weak to non-existent.

Therapeutic Medial Branch Blocks

In a series of prospective, randomized evaluations of repeated therapeutic MBB with LA, LA plus sarapin, LA plus steroid, and LA plus steroid and sarapin, Manchikanti et al. reported significant relief of lumbar,[238] thoracic,[239] and cervical facet pain,[240] in more than 85% of individuals in all groups for up to two years. Patients were screened with comparative LA blocks, but the studies lacked a placebo or sham group, and a large percentage of patients were on opioids. No differences were found with the addition of either steroids or sarapin to LA. Although a small percentage of patients may derive long-term benefits from diagnostic MBB either from a placebo response, from "breaking the cycle of pain," or, in rare instances, from the anti-inflammatory effects of steroids on a medial branch trapped beneath the MAL, most studies have failed to corroborate these findings.[137,185]

Several other studies have evaluated the therapeutic potential of MBBs. In a non-randomized, placebo-controlled study, Dias da Rocha et al.[241] found that in 52% of 104 patients who responded to lidocaine MBB, two-thirds experienced persistent relief at three months. However, older randomized trials comparing MBB to IA injections[148,186] found sustained benefit at 1 month in only a small percentage of patients. More recently, a large, well-designed placebo-controlled study comparing MBB with LA and steroids, IA injections with LA and steroids, and placebo injections found no significant difference between groups at the one month follow up, with only 11% of MBB patients experiencing at least a two point reduction in average back pain score.[105] The concept that blocking the medial branch with or without steroids can lead to sustained pain relief is also inconsistent with randomized controlled trials evaluating RFA in patients who responded to MBB with significant but short-term benefits. Among the several trials evaluating medial branch RFA that reported the number of patients who obtained persistent pain relief from MBB, only the study by Nath et al.[243] noted a substantial percentage of patients who obtained prolonged relief. Overall, the international facet joint guidelines assert that there is little supporting evidence for the prolonged benefit from MBB.[185]

Pulsed Radiofrequency of the Medial Branch and Facet Joint

Pulsed radiofrequency (pRF) is a non-invasive technique that has been used for the treatment of chronic pain. The conceptual appeal of pRF is that it acts via the creation of an electrical field, beneficial alterations in gene expression, and enhancement of descending modulatory systems, resulting in minimal nerve damage.[244] Unlike conventional RF, which injures nerves that can lead to deafferentation pain (in nerves containing A-β fibers), muscle weakness (in nerves containing motor fibers), and neuroma formation (which can result in ectopic discharges), pRF is frequently used as a treatment for neuropathic pain, in which nerve damage is the underlying cause of the pain.[245–250]

Two clinical trials compared the conventional RF with pRF. Kroll and colleagues[251] randomized 50 patients who achieved >50% relief after two MBBs to continuous RF or pRF. Although no significant differences between groups were found at the three month follow up, a comparison of within-group differences revealed greater improvements in pain and disability in conventional RF patients. This study was underpowered to detect between-group differences. In the second study, Tekin et al.[252] randomized 60 patients with a positive response to a single MBB to either sham RF (LA only), pRF, or continuous RF. All groups, including the LA only group, showed improvements in pain and disability. However, the magnitude of improvement and duration of benefit was significantly greater in the continuous RF group. A randomized, double blind study was conducted by Çetin et al.[253] comparing continuous radiofrequency neurotomy to pRF in 118 patients with injection-confirmed lumbar facet joint pain. The authors found that continuous radiofrequency was superior to pRF in both the short and long term for pain reduction and satisfaction. In summary, the current state of evidence does not support pRF in the treatment of facet joint pain.

Radiofrequency Denervation (see also Chapter 66 Radiofrequency Treatment)

Although percutaneous rhizotomy was first described by Rees in 1971,[255] the technique of percutaneous RF lesioning is generally credited to the neurosurgeon Norman Shealy.[256,257] For lumbar facet RF denervation, most studies report sustained relief in 50%–80% of patients without previous back surgery,[158,258] whereas 35%–50% of subjects with failed back surgery syndrome obtain prolonged relief.[158,259–261] In the only study comparing outcomes of cervical z-joint denervation in operated and non-operated spines, Cohen et al. found no difference in success rates between patients with failed neck surgery syndrome and those who had never undergone surgery.[157] Reasons by which prior surgery might predispose patients to treatment failure include altered anatomy, greater baseline disease burden including opioid use, and a higher incidence of false positive diagnostic blocks.[185]

Lumbar Radiofrequency Neurotomy

Several randomized and numerous uncontrolled studies have evaluated the effectiveness of lumbar and cervical radiofrequency neurotomy and reported variable results. These studies are summarized in Table 31.5.

A key flaw in many studies is the failure to select patients based on placebo-controlled or even comparative LA blocks, which are now acknowledged to be inferior to placebo controls. Although double blocks are often impractical and will inevitably result in a lower overall success rate with a higher total cost, elimination of "false positive" responders is ideal for studies that seek to establish efficacy. Because the anatomy of the lumbar spine makes it more difficult to position electrodes to create large lesions that enhance the likelihood of capturing the target nerve, practitioners should ideally insert the cannulas at a sharp cephalad-medial angle so that they are situated near parallel to the medial branches. In most randomized trials evaluating lumbar facet RFA, electrode positioning was suboptimal, including the Leclaire,[193] Gallagher,[192] van Kleef,[195] van Wijk[194], and MINT studies.[262] However, some may construe these findings as evidence that RF denervation is a fundamentally flawed treatment. A more plausible interpretation is that they indicate a strong need to optimize RF denervation techniques and better identify candidates likely to obtain positive outcomes. Among randomized studies, those that have employed more stringent selection criteria (i.e. lower enrollment rates) and utilized optimal lesioning strategies are more likely to report positive outcomes.

Thoracic Radiofrequency Neurotomy

As noted above, an older observational study performed in 40 patients reported an 83% success rate for thoracic medial branch RFA at a mean follow up of 31 months.[263] Other small, retrospective studies have reported success rates of 40% and 68% at variable follow ups. The main challenge with thoracic facet RFA is the highly variable locations of the thoracic medial branches.[41] This is one reason aggressive lesioning strategies such as bipolar RFA, cooled RFA, and creating multiple lesions have been advocated.[264,265]

Cervical Radiofrequency Neurotomy

Only three randomized, double blind trials have evaluated percutaneous RF denervation for cervical facet pain (Fig. 31.7). Lord et al. randomized 24 patients with whiplash injury following an MVA and a positive response to diagnostic, placebo-controlled cervical MBB to receive either cervical medial branch denervation or a sham procedure.[129] Patients with pain stemming solely from the C2-3 z-joint were excluded. A series of three blocks were performed to diagnose cervical facet pain, including a placebo block. A block was deemed positive if the patient had complete, concordant relief each time an LA was used but no relief with saline. At each level, two to three lesions were created. The mean time for a return to 50% of baseline pain was 263 days in the RF group and eight days in the placebo group. At 27 weeks, seven patients in the RF group and one patient in the control group remained pain free. Five of the patients in the RF group had numbness in the territory of the treated nerves, but none considered it troublesome.

In a 2004 study, Stovner et al.[266] randomized 12 patients in whom cervicogenic headache was diagnosed based on clinical symptoms to receive either cervical facet RF denervation or a sham procedure. Although the authors performed medial branch and greater occipital nerve blocks, the results were not used to select patients. The study was halted early secondary to the failure to enroll the subjects. At the three month follow up, four of six patients in the RF denervation group obtained a meaningful clinical response versus two of six patients in the sham group. At six months, no differences were noted between the groups. The results of sham denervation in this study are comparable to those of a previous uncontrolled study that evaluated RF for cervicogenic headache in which patients reported a 34% reduction in symptoms.[267] In 2021, van Eeerd et al. randomized 76 patients to cervical MBB with bupivacaine and sham RFA or medial branch RFA. Patients were selected based on clinical presentation and radiographic findings, without prognostic blocks. Through 6-month follow-up, the benefits favoring the RFA group for pain and patient global impression of change did not significantly differ from the MBB

TABLE 31.5 Outcomes Studies Assessing Medial Branch Radiofrequency Denervation for Lumbar, Thoracic, and Cervical Facet Joint Pain

Study, Year	Number and Type of Patients	Follow Up Period and Methodologic Scores	Results	Comments
Gallagher et al.[192] 1994	41 pts with chronic LBP who obtained "clear-cut or equivocal" relief from single intraarticular facet joint injections with LA and steroid. 18 pts with a good response and six pts with an equivocal response underwent RF denervation. 12 pts with a good response and five with an equivocal response underwent sham denervation.	• Six months • MQ = 2 • CR = 6	Significant differences in pain scores were noted only between patients with a good response to LA blocks who underwent true RF denervation (n = 18) and those with a good response who underwent sham treatment (n = 12) through six months.	Did not define "good" or "equivocal" response. Anatomic landmarks were not well described. Observers were not blinded. Electrode not placed parallel to the nerve. In "Methods" stated that only LA was used, but in abstract stated that LA and steroids were used
Lord et al.[51] 1996	24 pts (12 per group) with chronic neck pain after MVA. Included pts with a (+) response to placebo-controlled diagnostic blocks. Randomized to undergo true RF at 80°C for 90 s or 37°C (placebo treatment) between C3 and C7 according to response to diagnostic blocks.	• Three months (12 months in pts with persistent relief) • MQ = 5 • CR = 8	The mean time to return 50% of preoperative to pain was 263 days in the RF group and eight days in the placebo group. At 27 weeks, seven points in the RF group and one in the control group remained pain free.	Excluded pts with solely C2-3 facet pain. Five pts in the RF group reported numbness in the territory of treated nerves.
van Kleef et al.[195] 1999	Subjects were 31 pts with chronic LBP who obtained ≥50% pain relief after a single MBB (one dropout). Compared true denervation with sham.	• 12 months • MQ = 5 • CR = 8	After three months, nine of 15 pts in the lesion group vs. four of 16 in the sham group had ≥50% pain relief. At one year f/u, seven of 15 in the lesion group and two of 16 in the sham group had ≥50% relief.	Used 0.75 mL of injectate for diagnostic blocks. Electrode not placed perpendicular to the target nerve. Used multifidus rather than sensory stimulation to identify the medial branch. Used 60 s lesions.
Leclaire et al.[193] 2001	Subjects were 70 pts with chronic LBP who obtained "significant" pain relief lasting >24 h after a single intraarticular facet injection of lidocaine and steroid (four dropouts). Compared true denervation with sham.	• 12 weeks • MQ = 4 • CR = 8	At four weeks, there were modest improvements in Roland-Morris (P = 0.05) and VAS (P = NS) pain scores, but not the Oswestry score. No difference in any outcome measure at 12 weeks.	Did not define "significant pain relief" with diagnostic injection. Inclusion criterion of >24 h pain relief is inconsistent with the pharmacology of lidocaine. Performed two lesions, each for 90 s. Anatomic landmarks not noted. Electrode not placed parallel to the nerve.
Stovner et al.[266] 2004	12 pts with unilateral cervicogenic HA received comparative LA blocks and a greater occipital nerve block. Randomized to cervical facet RF or sham procedure.	• 24 months • MQ = 4 • CR = 7	At three months, four of six RF pts had a meaningful clinical response (≥30% improvement), as did two of the six in the sham group. Six months after the procedure, no differences were noted between groups.	The RF group had a better response to diagnostic blocks. Able to recruit only 12 pts in 2.9 years. Excluded pts with ongoing litigation. Diagnostic blocks were not used to select RF patients.
Van Wijk et al.[194] 2005	81 pts with chronic LBP who obtained ≥50% pain relief after two-level intraarticular facet injection of LA (no dropouts). Compared true denervation with sham.	• 12 months • MQ = 5 • CR = 7	No significant difference at three months for combined outcome measure (pain score, physical activity, and analgesic intake). The global perceived effect was greater in the treatment group at three months.	Improvement in pain scores persisted throughout the 12 month f/u. Used 60 s lesions.

TABLE 31.5 Outcomes Studies Assessing Medial Branch Radiofrequency Denervation for Lumbar, Thoracic, and Cervical Facet Joint Pain—cont'd

Study, Year	Number and Type of Patients	Follow Up Period and Methodologic Scores	Results	Comments
Tekin et al.[252] 2007	60 chronic LBP pts with ≥50% relief from a single MBB at either L1-3 or L3-5 received either sham, pulsed RF, or RF denervation.	• 12 months • MQ = 4 • CR = 8	Continuous RF was better than pulsed RF and sham for pain. No significant difference between sham and pulsed RF. Regarding improvement in disability, continuous RF and pulsed RF were better than sham.	Used 0.3 mL diagnostic MBBs. The proper technique was used for MBB and RF.
Nath et al.[243] 2008	40 pts with chronic LBP with ≥80% relief from three LA facet blocks.	• Six months • MQ = 4 • CR = 6	RF group fared better than the control group for all outcome measures, though benefits were modest.	40 of the 376 screened were randomized. Created six empirical lesions without stimulation.
Civelek et al.[271] 2012	100 patients with LBP were randomized to receive a medial branch block or radiofrequency neurotomy.	• 12 months • MQ = 2 • CR = 4	Medial Branch block was more effective at one month than radiofrequency, but at six and 12 months, RFA pts had better results.	Myriad methodologic flaws including lack of blinding, suboptimal RF technique, and lack of prescreening with diagnostic MBB.
Lakemeier et al.[242] 2013	56 patients with axial LBP were randomized in a double blind fashion to intraarticular steroids with sham RFA or medial Branch RFA.	• Six months • MQ = 1 • CR = 4	Both intraarticular and RFA groups improved with no significant differences between them.	Methodologic flaws in the study included intraarticular block rather than MBB screening; suboptimal RFA technique; permitted analgesic co-interventions.
Moussa et al.[272] 2016	A prospective randomized controlled trial where 120 patients with injection-confirmed lumbar facet joint pain were randomly divided into three groups: radiofrequency coagulation of the facet joint capsule, radiofrequency denervation of the medial branches, and sham radiofrequency lesioning.	• Three years • MQ = 4 • CR = 8	Both RF groups > control group. RF of the facet joint capsule = RF of the medial branches through 1-year, but superior to RF of the medial branches after one year.	Use of RFA not validated for capsular denervation. All groups also received a local anesthetic and steroid injection. Two lesions were created in the capsule, three along the medial branches. Used small electrodes with a short heating time.
Van Tilburg e al.[273] 2016	A randomized placebo-controlled double blind multi-center trial was performed in 60 patients with chronic LBP. The active group was treated with radiofrequency and the sham with lidocaine and placebo RFA.	• Three months • MQ = 4 • CR = 6	No difference between groups.	Required less than 50% pain relief for a positive block; 79% of blocks positive. Suboptimal technique (perpendicular electrode orientation, short heating time). Permitted co-interventions.
Juch et al.[262] 2017	The MINT study consisted of three pragmatic multi-center, nonblinded randomized clinical trials that evaluated the effectiveness of RFA treatments for participants with chronic LBP. The facet joint trial contained 251 participants.	• 12 months • MQ = 3 • CR = 6	Radiofrequency denervation combined with a standardized exercise program resulted in no clinically important improvement in chronic LBP compared with a standardized exercise program alone.	Myriad flaws included >70% positive rate for diagnostic blocks, that patients with a negative block in one study proceeded to blocks for another study, permitted psychological and exercise co-interventions, and suboptimal technique.

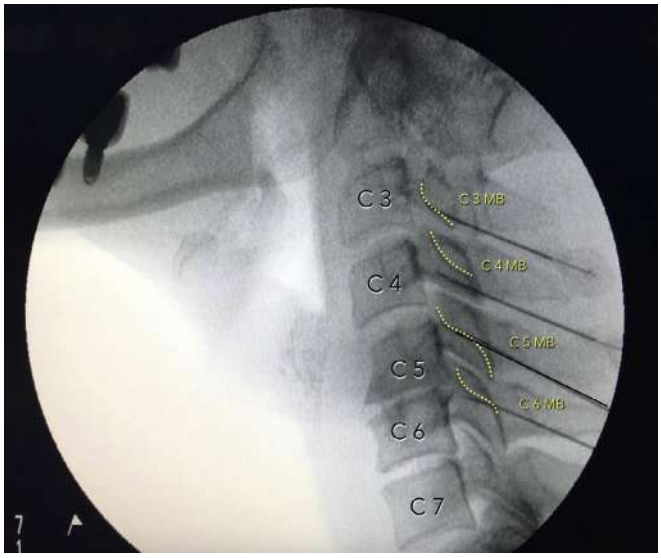
Continued

TABLE 31.5 Outcomes Studies Assessing Medial Branch Radiofrequency Denervation for Lumbar, Thoracic, and Cervical Facet Joint Pain—cont'd

Study, Year	Number and Type of Patients	Follow Up Period and Methodologic Scores	Results	Comments
Kennedy et al.[225] 2018	This double blind, controlled trial randomized 24 patients to receive intraarticular corticosteroid (triamcinolone 20 mg) or saline via fluoroscopic guided injection.	• Six weeks • MQ = 4 • CR = 8	Corticosteroid injections into the lumbar facet joints were ineffective in reducing the need for radiofrequency neurotomy of the medial branches in those with facet joint pain confirmed by comparative medial branch blocks.	Pain scores and function were not recorded. Diagnostic MBB was performed with 0.2 mL.
Cohen et al.[105] 2018	This multi-center randomized study randomized 229 patients in a 2:2:1 ratio to receive intraarticular facet injections with bupivacaine and steroid, medial branch blocks, or saline.	• Three months • MQ = 5 • CR = 9	No long-term benefit for intraarticular steroids or MBB. Individuals who received MBB or IA injections had a greater reduction in pain after RFA.	This study confirmed the lack of long-term efficacy for intraarticular and medial branch facet blocks but supports their use as prognostic tools.

The methodologic quality (MQ) score was based on the five point Jadad scale.[223] A score of three or greater indicates high methodologic quality. The clinical relevance (CR) score was based on patient selection parameters and description of the RF technique (zero to nine scale) as described by Geurts and colleagues.[319]

f/u, Follow up; *HA*, headache; *LA*, local anesthetic; *LBP*, low back pain; *MBB*, medial branch block; *MVA*, motor vehicle accident; *NS*, not significant; *pts*, patients; *rec'd*, received; *RF*, radiofrequency; *VAS*, visual analog scale.



• **Figure 31.7** Lateral view of obliquely-placed electrodes targeting the cervical medial branches. Note that the electrodes are inserted in a cephalad direction in the center of the articular pillar, after which they may be adjusted based on stimulation parameters. *MB*, Medial branch.

group, but the benefits lasted longer (median duration of benefit 42 vs. 12 months).[268] In an open-label prospective study comparing cervical z-joint RF results between litigant and non-litigant patients with whiplash injuries, Sapir and Gorup found no significant differences between groups in one year outcomes.[269] Potential reasons for limited RF success rates for chronic neck pain and cervicogenic headache include technical difficulty denervating the frequently affected C2–3 facet joint, concomitant sources of head pain, and lack of specificity for diagnostic injections. As noted above, the higher pre-test probability of neck pain arising from the facet joints (i.e. lower false positive rate and higher false negative rate) and a greater likelihood of nerve capture during RFA (electrodes can be placed parallel to the nerve in a smaller area) have led some investigators to forego any diagnostic blocks. As a prelude to their randomized, controlled trial that did not utilize prognostic blocks, van Eerd et al.[270] performed a retrospective review of 65 patients who underwent a modified posterolateral RFA procedure based solely on clinical findings. The rationale for performing RFA without a diagnostic block is based on 1) the lower false positive rate in the cervical spine because of a higher prevalence rate of facetogenic pain in individuals with neck pain than in those with LBP; 2) the lower variability in location for the cervical than the lumbar medial branches; and 3) the greater ease in targeting them with electrodes oriented parallel. The authors reported a 55% success rate at the two month follow up. However, in their follow up sham-controlled trial using the same approach, the authors found no significant differences between the group that received RFA and those who received medial branch blocks and placebo RFA, through with both groups achieving >50% success rates.[268]

Outcome studies on cervical radiofrequency denervation are summarized in Table 31.5.[271–273]

Use of Neurostimulation

Generally, a threshold of 0.5 V or less is deemed sufficient to create a lesion that encompasses the target nerve, although the margin of error can be increased using techniques that enhance lesion size. Although sensory stimulation may indicate close proximity to the target nerve at this voltage, many patients perceive concordant stimulation at 0.5 V or less even when the electrode is purposefully placed in muscle, as during a sham procedure. In a prospective study involving 61 patients, Cohen and colleagues[274] found no correlation between the mean sensory threshold and lumbar RF denervation outcomes. Although one might construe this to mean that sensory stimulation is not necessary, it should be emphasized

that sensory thresholds in these patients were recorded only after repeated electrode adjustments. In addition to nerve proximity, other factors that can affect sensory stimulation include age, sex, inherent pain perception, analgesic therapy, the use of sedation, and the presence of comorbidities such as diabetes. An alternative or complement to sensory stimulation in the lumbar and cervical spine regions is to elicit multifidus or other paraspinal muscle contraction since the medial branch that innervates the lumbar facet joint also supplies this paraspinal muscle. The 2020 International Lumbar Facet Joint guidelines[185] provided a grade C recommendation for sensory stimulation and a grade B recommendation for motor stimulation. In the cervical spine, there is a reported case of permanent head drop in a patient who underwent bilateral cervical medial branch RFA without the use of motor stimulation.[275]

Meta-analysis on Radiofrequency Denervation

Several meta-analyses of radiofrequency denervation have reached different conclusions. A meta-analysis published in 2014 by Poetscher et al.[276] concluded that RFA of lumbar facet joints was more effective than placebo and possibly more effective than steroid injections. A 2015 Cochrane systematic review by Maas et al.[277] concluded that there was no high quality evidence suggesting that RF denervation provides pain relief or functional improvement in patients with chronic LBP. They also found that the quality of evidence for RF denervation in chronic LBP ranged from very low to moderate. In 2017, a meta-analysis by Lee et al.[278] concluded that conventional radiofrequency denervation resulted in significant reductions in LBP originating from the facet joints in patients with a positive response to diagnostic blocks over 12 months when compared with sham procedures or epidural nerve blocks. Manchikanti et al. performed several systematic reviews evaluating cervical[279] and lumbar[280] facet radiofrequency denervation. In the cervical spine, the authors concluded that there was level II for the long-term effectiveness of radiofrequency neurotomy. In the lumbar area, they found moderate evidence supporting radiofrequency neurotomy for chronic LBP.

Another comprehensive systematic review published by Schneider[281] in 2019 sought to determine the effectiveness of lumbar medial branch thermal radiofrequency neurotomy based on different selection criteria and procedural techniques. The authors found that the best outcomes were achieved when patients were selected based on high degrees of pain relief from dual medial branch blocks, using a technique employing parallel electrode placement.

Factors Associated With Outcome

In a multi-center study, Cohen et al. identified factors associated with successful RF treatment in 192 patients who underwent lumbar facet denervation after a single positive MBB.[158] Among the 15 variables analyzed, only paraspinal tenderness was found to predict successful treatment. Factors associated with failed treatment included increased pain with hyperextension and axial rotation (i.e. facet loading), duration of pain, and previous back surgery. The latter two variables have been associated with treatment failure for RF denervation and a host of other LBP interventions including epidural steroid injections and surgery.[282–284] A study performed on the cervical spine by the same group of investigators found similar results. The only variable associated with a positive outcome was paraspinal tenderness. Factors associated with a negative outcome included opioid use, radiation to the occiput, and pain worsened by extension rotation maneuvers.[157] Streitberger et al.[285] performed a prospective study in 275 individuals and found that depression was associated with a shorter duration of benefit after lumbar medial branch RFA. In a retrospective study involving 111 people by Conger et al.,[286] the authors found that a larger Cobb angle and older age foretold lumbar medial branch RFA treatment success. More recently, Cohen et al.[287] performed a prospective observational study in 318 patients to determine predictors of treatment results for minimally invasive low back interventions in general, including medial branch RFA. They found that older age, shorter duration of pain, lower baseline pain scores and functional disability, absence of secondary gain, absence of concomitant pain and psychiatric conditions, and having less non-organic (Waddell) signs were associated with treatment success. A negative correlation between Waddell signs and facet treatment outcomes was previously reported by Lilius et al.[219] for lumbar facet intraarticular steroid injections.

Repeating Radiofrequency Denervation

When pain returns following RF denervation, which typically occurs between six months and one year, neurotomy can be repeated with similar efficacy.[288,289] In the cervical spine, the success rate for repeated RF denervation may be slightly higher than that in the lumbar spine. One systematic review reported a 59% success rate for repeat lumbar medial branch RFA based on two studies and an 88% repeat success rate for cervical medial branch RFA based on five studies.[290] The international lumbar facet guidelines[186] recommend repeating lumbar facet RFA in individuals who obtain at least three months of meaningful relief, up to twice per year, without repeating the prognostic block if the recurrence is similar to the pre-RFA pain pattern.[185]

High Intensity Focused Ultrasound Ablation and Other Novel Forms of Denervation

An alternative approach to RFA is high intensity focused ultrasound (HIFU) ablation, guided by magnetic resonance.[291,292] HIFU is a novel non-invasive technique whose target point is the entire facet surface, whereby nerve endings terminate to innervate the joint. Advantages of this technique include its non-invasive nature and that it does not entail radiation exposure.[293] Several other non-radiofrequency mediated forms of denervation have been described, including laser irradiation,[294] cryoablation,[295] and phenol, and alcohol injection,[296] some of which are limited by their lack of precision, which can theoretically result in extravasation of neurolytic substances into the intervertebral foramen, which can lead to numbness and/or weakness. However, there have been no randomized trials evaluating efficacy.

Surgery

Surgery is occasionally performed to treat facet arthropathy despite a lack of evidence supporting fusion for degenerative spinal disorders.[297,298] Not surprisingly, the results of studies evaluating the use of lumbar z-joint blocks to predict outcomes of lumbar arthrodesis are discouraging. The three studies that compared surgical outcomes between facet block responders and non-responders failed to show a difference between groups.[299–301] Bough and associates[131] conducted a retrospective review of 127 facet joints surgically removed from 84 patients in an attempt to correlate histologic evidence of facet degeneration with a provocative response to preoperative facet arthrography. Although the authors found the positive predictive value of concordant pain reproduction to be 85%, the negative predictive value was only 43%, which led them to conclude that provocative facet arthrography was of little value as a presurgical screening tool. In a prospective case series,

Lovely and Rastogi[302] found that 83% of 23 patients who responded to bracing and three facet blocks achieved 90% or greater pain relief after fusion surgery at the latest follow up. However, the large volumes used per block, the failure to exclude placebo responders, and the lack of a comparison group undermine the conclusions that can be drawn. Patients with lumbar z-joint pain might respond to arthrodesis because some surgeons, either purposefully or inadvertently, perform medial branch rhizotomies during pedicle screw placement. More recently, percutaneous fusion and open facet arthroplasty[303] have recently been used to treat facet joint pain, but there are no prospective outcome data for either procedure. In summary, there is no convincing evidence to support any surgical intervention for lumbar z-joint pain other than that resulting from a traumatic dislocation.

Complications

Serious complications are uncommon after facet interventions.[304] The metabolic and endocrine sequelae of intraarticular facet joint steroids have not been studied. However, based on extrapolation from epidural steroid injections, one would expect suppression of the hypothalamic-pituitary-adrenal axis for up to four weeks depending on the steroid used and elevated glucose levels for less than one week.[305,306] Although infrequent, a host of infections has been associated with intraarticular injections, including septic arthritis, epidural abscess, and meningitis, but these infections are rare following RF denervation.[307,308,309] Reports of spinal anesthesia and post-dural puncture headache have been published but are preventable using imaging in multiple views.[310,311]

A prospective study described complications associated with more than 7400 patient encounters and more than 43,000 individual facet injections in the cervical, thoracic, and lumbar spine,[312] with no serious complications reported. Intravascular injection was detected in 11.4% of patients overall, with the highest incidence in the cervical region (20%). In less than 1% of cases, patients experienced vasovagal reactions, bruising, and nerve root irritation. Catastrophic injuries have been reported, including a posterior circulation stroke during a C1–2 intraarticular steroid injection that was thought to be because of microvascular injury from accidental injection into the vertebral artery, and a case of head drop after bilateral cervical medial branch RFA.[275,313]

Numbness and dysesthesia have been reported after RF denervation but tend to be transient and self-limited. Burns are rare with RFA and may result from electrical faults, breaks in the insulation of electrodes, generator malfunction, and theoretically from the creation of large lesions in a thin individual with little soft tissue overlying the target nerve.[314] The most common complication following facet joint RF is neuritis, with a reported incidence of less than 10% in the lumbar spine but higher in the upper cervical spine.[315] In one study, the post-administration of corticosteroids or pentoxifylline was found to reduce the incidence of postprocedural pain following RF denervation.[316] However, a subsequent large retrospective study failed to find a reduction in neuritis in individuals administered post-RFA steroids vs. those who did not. Notably, one study found that steroids administered pre-RF lesioning reduced lesion size.[317,318]

Guidelines or Recommendations of Best Practice

Many pain societies have tried to establish guidelines to promote the best way to select patients and perform radiofrequency denervation. Below is a brief summary of the international working group guidelines for lumbar facet joint pain.[185]

1- Consensus Practice Guidelines on Interventions for Lumbar Facet Joint Pain From a Multispecialty, International Working Group

Authors: Cohen et al.

Societies: 12 international societies and the United States Depts. of Defense and Veterans Affairs

Designs: A modified Delphi method was used to answer 17 questions for guideline development. The USPSTF was utilized to grade the level of evidence and strength of recommendations.

Year: 2020

Recommendations:

1. There are no pathognomonic physical examinations or historical signs that can reliably predict the response to facet joint blocks in individuals with mechanical chronic LBP, although paraspinal tenderness may be weakly associated with a positive block.
2. There is weak or no evidence supporting the use of image tests for identifying painful lumbar facet joints prior to lumbar MBB or IA facet joint injections.
3. A three month trial of different conservative treatments is recommended before facet joint interventions.
4. CT or fluoroscopy (lower costs, faster time, and less radiation exposure than CT) is recommended for lumbar MBB. However, ultrasound may be helpful in patients in whom radiation exposure may be associated with potential harm (e.g. pregnancy) or in patients without obesity when radiographic or radiologic imaging is unavailable.
5. MBBs have limitations as a diagnostic tool related to aberrant lumbar facet joint innervation. They provide better predictive information for medial branch RF denervation than intraarticular injections.
6. MBB should be a prognostic screening test of choice before lumbar facet RFA. Intraarticular injections of corticosteroids may be of therapeutic value for certain populations in whom there is acute inflammation and in whom denervation may be relatively contraindicated but are unlikely to provide long-term benefit in most people.
7. Sedation should not be routinely administered for diagnostic or prognostic facet injections without reasonable indications.
8. Lumbar MBBs should be performed with ≤0.5 mL (total volume) to reduce spread to adjacent structures.
9. The routine use of therapeutic facet injections should be discouraged. However, in patients who are at risk of adverse consequences from RF denervation (e.g. young athletes, older individuals on anticoagulation therapy or with implantable cardiac devices) or in whom there is a strong likelihood of success (e.g. individuals who obtained prolonged relief from previous diagnostic injections with or without steroids), it may be reasonable to add steroids to a block to derive intermediate-term relief.
10. A ≥50% reduction in pain relief should be considered as a positive prognostic block to maximize access to care.
11. A single block is recommended as a prognostic block before RF denervation because of the significant false negative rate of blocks.
12. Creating larger lesions with reduced lesion variability may increase the likelihood of capturing the medial branch.
13. Near parallel placement of traditional electrodes (non-cooled electrodes) is recommended to maximize nerve capture.
14. Sensory stimulation is recommended when single lesions are anticipated; when multiple lesions are planned, the evidence for sensory stimulation is inconclusive. Motor stimulation should always be performed.

15. Recommendations for Avoiding Complications:
    a. Vascular penetration: Aspirating and visualizing the spread of contrast on real-time fluoroscopy while performing MBB can reduce false negative results. Non-heparin anticoagulants should be continued in the peri-procedural period for patients undergoing lumbar MBB or RF denervation.
    b. Procedural pain and numbness: Injection of steroids through the cannula after ablation may reduce pain and discomfort following RF denervation.
    c. Injury to the spinal cord or nerves: Adequate visualization of needles in true anteroposterior, oblique, and lateral views and absence of sensorimotor responses in a radicular distribution in response to test stimulation prior to RF may also reduce the probability of injury to the spinal cord and spinal nerve roots.
    d. Degeneration of spinal anatomy and musculature: Physical therapy regimens aimed at restoring the function of paraspinal muscles before and after RF denervation are recommended.
    e. Impact on implanted devices: Use of bipolar RF mode is preferable, along with consulting the device manufacturer and the specialist team that implanted the device.
    f. Tissue burns: Positioning large monopolar ground pads in an optimal location and orientation may prevent tissue burns.
    g. Impact on spinal instrumentation: Ensure that the RF cannula is not in contact with a pedicle screw to avoid thermal injury to tissues surrounding the implanted spinal hardware. Previous spine surgery is associated with a higher rate of false positive blocks and lower RFA success rate.
16. There should be different standards in selecting patients for radiofrequency ablation in clinical trials and clinical practice.
17. The lumbar medial branch RFA can be repeated on recurrence of baseline pain in patients who experience a minimum of three months of improvement (preferably six months improvement for multiple procedures) following a previous RF denervation.

Conclusions

Pain originating from the facet joints has long been recognized as a potential source of back and neck pain. The three most caudal lumbar facet joints, L3–4, L4–5, and L5–S1, are exposed to the greatest strain and are thus more prone to pathology. In patients with chronic neck pain, the C2–3 and C5–6 facet joints are most commonly affected clinically, while radiologic studies have shown that C3–4, C4–5, and C2–3 undergo the most degeneration. The exact prevalence of facet disease is unclear but maybe as high as 10%–15% in patients with axial LBP, 49%–60% in patients with chronic neck pain, and 42%–48% in patients with axial mid-back pain. By the age of 60 years, more than half of all symptomatic individuals will experience significant lumbar facet joint degeneration, with similar proportions in other spine regions.

No discrete historical data for physical findings are pathognomonic for facet arthropathy in any region. Paraspinous muscle tenderness appears to be the only physical examination finding reliably associated with a positive response to diagnostic blocks and RF of the medial branches; however, its specificity is unknown. The referral patterns for pain arising from the facet joints at different levels and different structures (e.g. facet joints and disks) overlap considerably. Reports on the correlation between CT and MRI evidence of facet arthropathy and the response to diagnostic lumbar facet blocks are conflicting. Since the facet joint is innervated by medial branches arising from the posterior rami of the spinal nerve at the same level and a level above the joint, LA blocks of these nerves have been advocated for diagnostic and prognostic purposes. Intraarticular facet injections with LA have been proposed as an alternative method for diagnosing facet joint pain, although the existing data suggest that MBB is a better predictive tool for RF denervation outcomes. Similar to other blocks, the potential for false positive and false negative results needs to be considered, and steps should be implemented to reduce their incidence.

Studies evaluating the long-term outcomes of RF denervation have demonstrated efficacy in well-selected patients.

Key Points

- Facet joints are an important source of axial spinal pain and are more common in individuals with neck and mid-back pain than in those with LBP.
- Facetogenic pain is often referred into the head, shoulder, and scapula in the cervical region, laterally in the thoracic region, and into the upper legs and sometimes groin in the lumbar region. There is a significant overlap between cervical facet levels and other spinal structures, such as the intervertebral discs.
- Facetogenic pain is more prevalent in elderly patients; in the cervical spine, whiplash is a common cause of facet joint pain.
- Facetogenic pain cannot be reliably identified using imaging modalities. Paraspinal tenderness is weakly predictive of response to facet interventions but has low specificity.
- Both medial branch blocks and intraarticular injections can be used to identify painful joints and select patients for radiofrequency ablation. There is some evidence that medial branch blocks are a better prognostic tool before radiofrequency ablation. Although intraarticular injections may theoretically confer greater diagnostic value than medial branch blocks, the high technical failure rate limits their utility.
- Steps that may reduce the false positive rate include limiting the volume of superficial anesthetic, avoiding procedural sedation, reducing block volumes, using a single-needle technique, and avoiding patients with poorly controlled psychopathology.
- Neither intraarticular injections nor medial branch blocks are likely to confer long-term benefits in a significant percentage of the population.
- To optimize access to care in light of the potential for false negative injections, more liberal selection criteria, such as using a single block and a 50% cutoff threshold, are recommended in clinical practice. In clinical trials, more rigorous criteria may be employed.

Suggested Readings

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Neurosurgical Approaches to Pain Management

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Neurosurgeons have a long history of surgical treatment for pain, particularly cancer pain. The notion that sectioning pain pathways could achieve pain control was first introduced by Spiller and Martin[1] in 1912, and was followed by the development of a whole array of surgical procedures aimed at interrupting ascending pain signals throughout different parts of the central nervous system.

Two major approaches are used when targeting the brain or the spinal cord to treat pain. The first is a nondestructive approach that uses either electrical stimulation of brain targets, which is thought to modulate the process of pain perception, or pharmacologic agents, which are introduced into the ventricular or intrathecal spaces to target pain-modulating receptors. Targets for electrical stimulation include the peripheral nerves, spinal cord, thalamic nuclei, periventricular gray (PVG) matter, periaqueductal gray (PAG) matter, and motor cortex. Currently, the pharmacologic agent of choice for intrathecal or intracerebroventricular (ICV) injection is morphine or other opiates. In general, nondestructive procedures are used for non-malignant pain. However, intrathecal opioids are also used for the treatment of cancer pain.

The second approach is a destructive approach, which is used with the goal of interrupting signals that lead to the perception of pain at various levels. Neuroablation can be performed on cellular complexes, such as nuclei or gyri, or on tracts to either disrupt the ascending sensory signals or destroy the limbic pathways involved in the emotional processes associated with pain.

This chapter discusses several approaches within the two broad categories of neurosurgical procedures for pain: (1) neuroablation and (2) neuromodulation, which is further subdivided into electrical and pharmacologic neuromodulation. Each broad category is further discussed based on the level of the nervous system that is being intervened.

Neuroablation

Cerebral Neuroablation

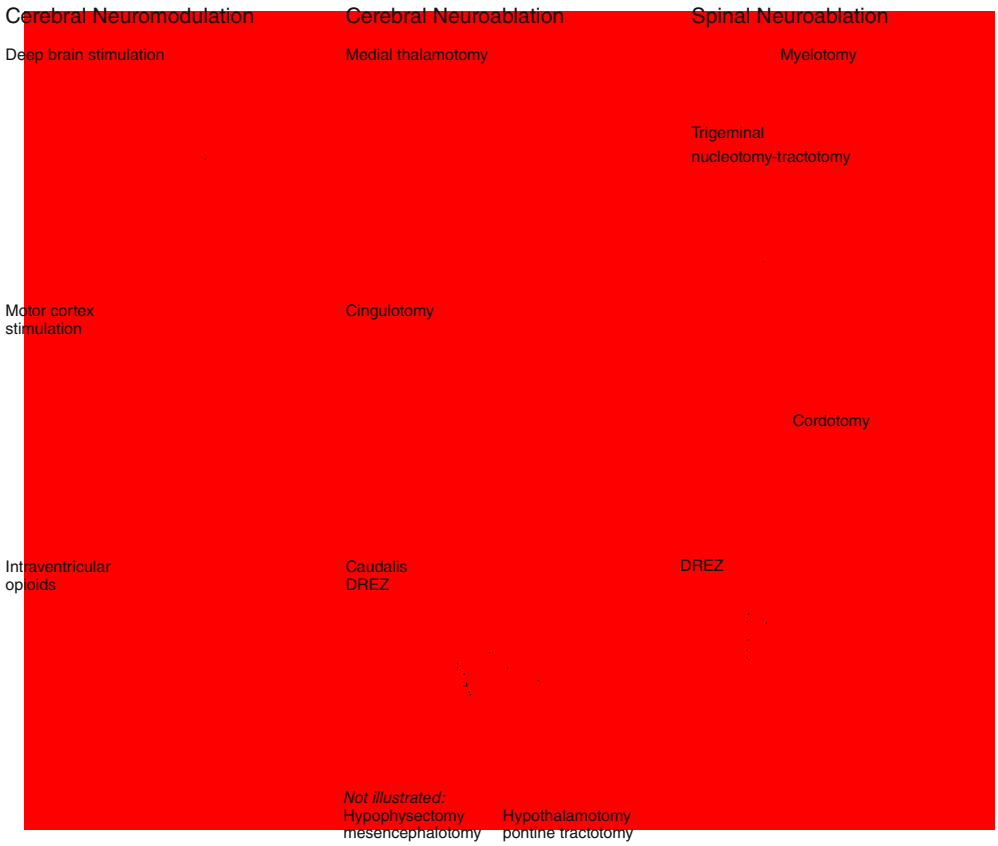
Historically, many procedures fall into this category, including mesencephalotomy, pontine tractotomy, and hypophysectomy. We focus on procedures that we believe have more than what could be considered purely historical significance.

Medial Thalamotomy

Stereotactic thalamic neuroablative surgery for pain is relatively safe with respect to deep brainstem structures, and because of the wide involvement of many thalamic nuclei in pain processing, it has been considered a part of the pain surgery armamentarium.[2] The first structure targeted for neuroablation was the ventral caudal (Vc) nucleus, as defined by Hassler.[3] However, it was soon recognized that neuroablation of the Vc nucleus was associated with significant deafferentation pain phenomena. The work of Mark and colleagues led to the belief that targeting the medial thalamic nuclei was more effective in managing pain.[4] Nuclear targets for neuroablative medial thalamotomy are (1) the centralis lateralis, (2) the centrum medianum, and (3) the parafascicularis. Several pain syndromes, including cancer pain, central and peripheral deafferentation pain, spinal cord injury, malignancy, arthritis, and neurogenic pain associated with Parkinson's disease, have been successfully treated by medial thalamotomy. Frank et al. reported the overall success rate of medial thalamotomy to be 52%,[5] with cancer pain being the main condition treated. Jeanmonod et al.[6] and Young et al.[7] used radiofrequency and gamma knife treatment, respectively, and reported a 60% success rate in achieving pain control. The ideal target lying between the three main medial thalamic nuclei (listed above) has yet to be determined, although the centrum medianum nucleus is the most frequently targeted. Deep brain stimulation (DBS) of the medial nuclei does not usually produce a conscious sensory response, and lesioning does not induce sensory loss. The published literature on medial thalamotomy is inconsistent regarding the target, guidance technique, patient population, and lesioning method used. Therefore the actual success rate of medial thalamotomy is challenging to assess. However, in general, the procedure is considered to be effective in treating nociceptive pain, with recent data pointing to some success in relieving neuropathic pain.

Stereotactic Cingulotomy

Cingulotomy refers to stereotactic lesioning of the anterior cingulate gyrus. Le Beau performed the first open cingulotomy to treat intractable pain in 1954,[8] which is believed to cause relief by altering a patient's emotional reaction to painful stimuli by interrupting the Papez circuit[9] and increasing tolerance to the subjective and emotional feelings of pain.[10,11] Cingulotomy is performed with standard stereotactic protocols, usually under general anesthesia. Bilateral lesions are made in the anterior aspect of the cingulate gyrus, and the success of the procedure is directly related to the extent of ablation of the cingulum (Fig. 32.1).[1] A suitable stereotactic cingulotomy candidate is a terminally ill patient with widespread metastatic disease that has extended to



• **Figure 32.1** Diagrammatic representation of cerebral neuromodulation and neuroablation procedures and spinal neuroablation procedures. *DREZ*, Dorsal root entry zone. (Adapted with permission from Raslan AM, McCartney S, Burchiel KJ. Management of chronic severe pain: spinal neuromodulatory and neuroablative approaches. *Acta Neurochir Suppl*. 2007;97:33-41. With kind permission from Springer Science and Business Media.)

the musculoskeletal system, where intrathecal or intraventricular administration of opiates is difficult. Emotional factors associated with pain would favor the selection of a stereotactic cingulotomy procedure. Stereotactic cingulotomy has been used to treat nonmalignant pain with a success rate of approximately 25%.[12] Stereotactic cingulotomy involves the ablation of sufficient anterior cingulate gyrus volume, which is usually achieved by producing at least two lesions with a wide surface area and non-insulated tip electrode. The procedure is generally safe, with few minor side effects. Pillay and Hassenbusch reported on a series of 12 patients in whom seven had satisfactory pain relief.[13] Cingulotomy is rarely used today, mainly because of its narrow indication, advances in the medical management of terminal cancer patients, and the widespread use of neuroaugmentive procedures.

Caudalis Dorsal Root Entry Zone (Brainstem Level)

Following the introduction of stereotaxis in the 1960s, the use of open ablative brain and brainstem surgery was almost abandoned. Siqueira first reported the performance of the caudalis dorsal root entry zone (DREZ) procedure in two patients.[14] Gorecki et al. at Duke University[15,16] later adopted the technique and expanded its indications. In the caudalis DREZ procedure, the caudal portion of the spinal trigeminal nucleus, along with the overlying trigeminal tract, is destroyed. Similar to spinal DREZ surgery, the objective is to destroy the cells of second-order neurons thought to be hyperactive in trigeminal deafferentation pain, thereby achieving pain relief (Fig. 32.1). The main indications for the caudalis DREZ procedure are ophthalmic postherpetic neuralgia and trigeminal anesthesia dolorosa. In cases of neuropathic facial pain in which all other medical and surgical modalities are ineffective, the caudalis DREZ procedure may represent a last resort. The procedure is rarely performed, and potential risks include ipsilateral limb ataxia and weakness.

Spinal Neuroablation

The first report of surgical disruption of spinal pain pathways was presented by Spiller and Martin in 1912. They sectioned the anterolateral quadrant of the spinal cord to interrupt the transmission of pain signals via the spinothalamic tract (anterolateral system) and to relieve pain on the contralateral side of the body caudal to the lesion.[1]

Several decades ago, open surgical sectioning of the spinothalamic tract (anterolateral cordotomy) to control pain was a common procedure in many neurosurgical centers. The procedure is mainly used to treat somatic nociceptive pain, usually from cancer. However, factors such as the debilitated state of cancer patients resulting in poor tolerance of open spinal cord surgery, together with high complication rates, meant that the procedure was not an ideal solution to the problem of cancer pain.

Currently, spinal cord targets for destructive procedures to treat pain include (1) the *spinothalamic tract* (anterolateral column), where destruction can alleviate somatic nociceptive pain below the level of the neck (e.g. anterolateral cordotomy), (2) the *trigeminal*

spinal nucleus, which is disrupted to treat trigeminal neuropathic pain (e.g. trigeminal tractotomy-nucleotomy ["caudalis DREZ"]), (3) the *midline ascending polysynaptic visceral pain pathway*, which is used to treat visceral pain, particularly pelvic pain (i.e. midline myelotomy), and (4) the DREZ, primarily to treat deafferentation pain in the upper extremity (i.e. DREZ procedure; Fig. 32.1). The role of each of these procedures in contemporary surgical pain management is reviewed.

Anterolateral Cordotomy

Anterolateral cordotomy refers to lesioning, sectioning, or other disruption of the lateral spinothalamic tract (LST), which is located in the anterolateral quadrant of the spinal cord. The procedure was historically performed in the upper thoracic spine via an open posterior approach and, less commonly, high in the cervical spine.[17] The spinal cord anterolateral ascending pain transmission system carries information about pain and temperature from one side of the body. The tract is formed by the central processes of nociceptive neurons in the dorsal horn that cross the spinal cord in the anterior commissure, ascend in the anterolateral column to the brainstem, and relay in the thalamus. Lesions of the anterolateral tract produce a contralateral deficit in pain and temperature sensation in two to five segments below the level of the cordotomy. Fibers in the LST have a somatotopic arrangement, with the sacral segments arranged posterolaterally and the cervical segments anteromedially.[18] The corticospinal (pyramidal) tract lies posterior to the LST with the white matter in between. The ventral spinocerebellar tract overlies the LST, and a lesion that damages the spinocerebellar tract may cause ipsilateral ataxia of the arm. Autonomic pathways for vasomotor and genitourinary control and reticulospinal fibers that subserve ipsilateral automatic respiration are also part of the anterolateral quadrant of the spinal cord. A patient with hemibody somatic cancer pain localized caudal to the cervical and upper thoracic areas represents the best candidate for a cordotomy procedure.[19]

From the beginning of the 20th century until the late 1960s to early 1970s, cordotomy was an open procedure undertaken at the mid to high thoracic levels since these sites largely avoided the complications of upper limb ataxia and sleep apnea.[20] Introduction of the minimally invasive percutaneous approach for cordotomy by Mullan et al. mitigated some of the neurologic risks and made it possible for the procedure to be performed on patients in poor general health.[21,22] In the mid-1980s and early 1990s, advances in opioid pharmacology, as well as the introduction of reversible and testable neuroaugmentive techniques, reduced the perceived need for spinal destructive procedures for pain control and led to a major reduction in the number of cordotomies performed by neurosurgeons worldwide. These neuroaugmentive procedures are expensive, particularly given the short life expectancy of many of the candidates, and are not uniformly effective.

Kanpolat et al. first introduced the concept of computed tomography (CT)-guided cordotomy, which allowed for a safer, selective, and more effective procedure.[23–25] In 1995, Fenstermaker and associates[26] performed anterior CT-guided lower cervical cordotomy through the disk space to avoid sleep apnea (a modification of Gildenberg et al.'s anterior low cervical percutaneous cordotomy).[27] CT-guided cordotomy is typically performed as a percutaneous procedure via a lateral approach to the spinal cord at the level of C2. However, the anterior cervical transdiscal approach can also be used; in a clinical study, this approach was used to control cancer pain in six of eight patients with pulmonary-pleural malignancy while avoiding sleep apnea.[28]

Currently, the CT-guided cordotomy procedure involves lumbar puncture and injection of a water-soluble dye into the patient's intrathecal space. After 30 min, a cervical CT scan was performed. These and subsequent scans were used to direct the cordotomy electrode into the anterolateral quadrant of the ipsilateral spinal cord. The electrode is insulated throughout the entire shaft except for the tip (2 mm in length and 0.3 to 0.4 mm in diameter). After measurement of the skin-dura distance and local anesthesia of the lateral cervical region, an electrode was introduced from the lateral side of the neck opposite the C2 foramen into the anterolateral quadrant of the spinal cord. Electrophysiologic testing is essential to ensure complete entry into the spinothalamic tract while avoiding the corticospinal tract. Radiofrequency lesions are performed until adequate hypoesthesia is achieved in the contralateral hemibody, or at least in the region of pain. CT-guided cordotomy has a higher success rate and fewer complications than traditional approaches. Control of cancer pain has been reported in more than 95% of the cases. Procedural complications may include weakness, hypotension, dysesthesia, mirror-image pain, ataxia, incontinence, and sleep apnea. Contemporary CT-guided cordotomy complications tend to be both minor and transient.[29]

An evidence-based review concluded that the case for cordotomy is somewhat unique among all cancer pain procedures in that it has the most supportive evidence.[30] The review used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system, and a recommendation for cordotomy was given. The GRADE system produces recommendations that are independent of the level of evidence.[31]

Trigeminal Tractotomy-Nucleotomy (Spinal Level)

Sensory information from the 5th, 7th, 9th, and 10th cranial nerves is carried by the trigeminal tract and branches into the trigeminal tract spinal nucleus. It extends caudally into the spinal cord to C2.[32] The trigeminal tract is considered a target for surgical treatment of facial pain,[33] and the history of procedures with this target is similar to cordotomy in that initial open procedures evolved toward less invasive stereotactic operations. Crue et al. and Hitchcock developed a stereotactic technique to lesion the trigeminal tract and nucleus via radiofrequency, named trigeminal nucleotomy.[34,35] As with CT-guided cordotomy, CT is used when performing the trigeminal tractotomy-nucleotomy (TR-NC) procedure today. Indications include anesthesia dolorosa, postherpetic neuralgia, neuropathic facial pain, facial cancer pain, and either glossopharyngeal or geniculate neuralgia.[25,36] The procedure can be considered, in some ways, a mini-caudalis DREZ procedure. The nucleus caudalis DREZ operation involves the same concept as the TR-NC procedure but includes the destruction of the substantia gelatinosa (Rexed laminae II and III) of the nucleus caudalis. Pain relief from TR-NC is reported to be complete or satisfactory in 80% of cases. Complications include ataxia from injury to the spinocerebellar tract (usually temporary) and contralateral hypoalgesia if the spinothalamic tract is included in the lesion.[25,34,36,37]

Extralemniscal Myelotomy

The extralemniscal myelotomy (ELM) procedure was first described by Hitchcock, who initially aimed to destroy the decussating fibers of the spinothalamic tract in the anterior commissure of the spinal cord to control pain in the neck and both arms.[38] ELM was achieved by creating a lesion in the central medullary region at the cervicomedullary junction. Unexpectedly, the ELM procedure also seemed to control pain caudal to the level of the

lesion. Schvarcz added the term "extralemniscal" to "myelotomy" because of the contention that the lesion incorporated an ascending polysynaptic nociceptive pathway.[39] Subsequently, the presence of such a tract has been confirmed anatomically. Several authors have presented reports of midline "punctuate" ELM via open procedures to interrupt this pathway at various spinal cord levels. The polysynaptic ascending pathway is thought to carry visceral nociceptive information and lies deep to the midline dorsal column.[40–42] The concept of CT guidance, previously applied to cordotomy and TR-NC procedures, has also been applied to ELM by Kanpolat et al., thus developing the image-guided ELM procedure used today.[36]

ELM is currently conceived as a pain control procedure for pain of visceral origin, including pelvic malignancy or cancer pain in the lower part of the trunk and lower extremities with a predominant visceral pain component. The procedure appears to be safe. However, pain relief results are not as good as those achieved with cordotomy and TR-NC procedures.[17]

Dorsal Root Entry Zone Lesions

With the introduction of the gate control theory in the 1960s, attention was drawn to the spinal dorsal horn as the initial physiologic substrate for pain modulation.[43] The dorsal horn and DREZ were then reconsidered as targets for neuromodulation (spinal cord stimulation) and neuroablation. In 1972, Sindou first attempted cervical DREZ destruction for neuropathic deafferentation pain in the upper extremity secondary to brachial plexus avulsion.[44] Nashold et al. soon followed and introduced the use of radiofrequency lesions to perform DREZ disruption.[45] Laser and ultrasound have also been used to damage the DREZ.[46,47] When large-fiber afferents (touch, position sense) in peripheral nerves or dorsal roots are altered, there is a reduction in the inhibitory control of the dorsal horn.[48] This situation is presumed to result in the excessive firing of the dorsal horn neurons, which is thought to be the cause of deafferentation pain and can be controlled by DREZ lesioning.[49] The technical details of the procedure and its variants are beyond the scope of this chapter, but DREZ lesioning is performed as an open surgical procedure under general anesthesia and often accompanied by intraoperative neurophysiologic monitoring. Surgical candidates include patients with brachial plexus avulsion, Pancoast's tumor with brachial plexus invasion combined with a good general condition and reasonable life expectancy, pain caused by spinal cord or cauda equina lesions, and pain accompanying spasticity after plexus or cord injury.[44] A general prerequisite for the DREZ procedure is a lack of functional use of the limb where the DREZ procedure is performed because complete sensory denervation of the limb will render it functional even if there is residual motor power. When patients are carefully selected, and the lesions are accurately performed, the success rate can be as high as 90% (with follow up success rates reported for up to four years). Complications and side effects include cerebrospinal fluid fistula, meningitis, ataxia, increased neurologic deficits, and dysesthesias.[50]

Neuromodulation

Electrical Neuromodulation

Central Electrical Neuromodulation

Deep Brain Stimulation

Pool first observed and reported on the analgesic effects of septal stimulation in the frontal and lateral forniceal columns while performing psychosurgery in the 1950s.[51] Heath and Mickle and Pool et al. subsequently reported the pain-relieving effect of septal and near-septal stimulation in nonpsychiatric patients.[52,53] Mazars and coauthors and Reynolds first reported pain relief from thalamic stimulation in 1960.[54,55]

Neurostimulation of the brain to relieve pain was thus introduced decades before what has become the main contemporary indication for DBS, that is, the treatment of movement disorders.[56] However, these early reports only set the stage for the eventual application of DBS for pain relief. In the mid-1960s, Melzack and Wall's gate theory[43] provided a logical rationale for DBS of the sensory thalamus to control pain. Shortly afterward, Reynolds reported on the analgesic effect of focal brain stimulation in rats (stimulation produced analgesia).[55] In the early 1970s, Hosobuchi and associates[57,58] and Richardson and Akil[59,60] were the first to report on stimulation of the human thalamus and PVG and PAG matter for pain control. Although stimulation of the thalamic sensory nuclei produced paresthesia in painful areas, consistent pain relief was not achieved. Similar results were produced by stimulation of the internal capsule.[61,62] Stimulation of the PVG and PAG typically did not produce paresthesia but did induce a sense of "warmth." High-intensity PVG/PAG stimulation produced unpleasant and sometimes overwhelming sensations, such as those of impending doom or terror. The centromedian-parafascicular complex was also targeted by Andy[63] as a stimulation site to treat pain, and this stimulation likewise did not produce paresthesia.

Despite reports describing the use of DBS to treat chronic pain in the 1970s and the early 1980s, data to support the technique never reached contemporary evidentiary standards. The use of DBS for pain control has failed to gain much acceptance in the neurosurgical community, and the use of DBS electrodes as pain control implants has never achieved United States Federal Drug Administration (FDA) approval. The lack of data to support the procedure is due, in part, to the small number of patients treated, inconsistent target localization, heterogeneity of the pain diagnoses treated, and failure to mount a prospective randomized trial that was sufficiently powered to answer the question of efficacy. The mechanism of pain relief by DBS is poorly understood but appears to be dependent on the site. The thalamus and PVG/PAG are the most commonly[64] targeted sites for DBS implants for pain. Hosobuchi et al.[58] suggested that the pain-relieving effect of PVG and PAG stimulation might involve endogenous opioid receptors based on their studies that found that the pain-relieving effect of DBS could be reversed by naloxone. Evidence supporting this mechanism of action of PAG/PVG DBS is inconsistent. Some investigators supported this concept, whereas others disagreed. Currently, it is postulated that the pain-relieving effect of PAG/PVG DBS is because of activation of multiple supraspinal descending pain modulatory systems, both opioid and nonopioid.[64] Pain relief resulting from stimulation of the ventral posterolateral (VPL) nucleus and ventral posteromedial (VPM) nucleus (Vc nucleus in the European Hassler terminology), the major sensory nuclei of the thalamus, is poorly understood. Inhibition of spinothalamic tract neurons[65] and activation of dopaminergic mechanisms have both been proposed.[66] The most accepted hypothesis is that thalamic stimulation activates the nucleus raphe magnus of the rostroventral medulla, which results in activation of a suprasegmental descending endogenous pain inhibition system.[64]

Meticulous patient selection, with classification of pain (i.e. nociceptive or neuropathic) and informed DBS target selection, should help improve the outcome of DBS for pain. Clinical case series (class III evidence) observations suggest that PVG/PAG

stimulation seems more effective in treating somatic nociceptive pain. This is consistent with the opioid-mediated effects of PAG/PVG stimulation. It has also been suggested that VPL and VPM (Vc) stimulation is more effective in treating neuropathic pain, a gate theory-based concept.[67] In the absence of controlled trials to prove efficacy, definitive conclusions regarding the ideal target for any particular pain syndrome remain elusive. Furthermore, many patients have mixed neuropathic/nociceptive pain, which suggests that the DBS target to control pain should be individualized according to the patient. Some authors have suggested placing two electrodes simultaneously in the sensory thalamic nucleus (Vc) and the PVG.[68] Another target, the anterior cingulate nucleus, has been tested and may produce better overall results.[69,70]

For some pain syndromes (e.g. thalamic infarction-induced pain), target selection is simpler, given that thalamic stimulation is impossible.[70] Chronic neuropathic pain conditions treated by DBS include anesthesia dolorosa, post-stroke pain, thalamic pain, brachial plexus avulsion, postherpetic neuralgia, postcordotomy dysesthesia, spinal cord injuries, and peripheral neuropathy pain. Nociceptive pain conditions treated by but not limited to DBS include failed back surgery syndrome, osteoarthritis, and cancer pain.[71]

Another target of interest for patients with post-stroke pain is the ventral striatum/anterior limb of the internal capsule.[71] Unfortunately, a recent randomized study failed to achieve a >50% decrease in pain compared to the control (sham) population. However, upon further analysis, the researchers showed significant improvement in the affective sphere of pain.[72]

DBS for chronic pain is similar to DBS for other indications (movement disorders) in that surgeons have several targets that are applicable to the general problem (Fig. 32.1). DBS target locations are often indirectly derived from the Schaltenbrand and Bailey atlas or measured directly from the patient's CT or magnetic resonance imaging scans. The location of these targets can be confirmed intraoperatively by macrostimulation, microelectrode mapping, or intraoperative imaging. To best judge the benefits of stimulation and help fine-tune stimulation parameters following final electrode implantation, a trial period of approximately one week is often a prerequisite. The complications of DBS for pain relief are similar to those of movement disorders. Typically, they are related to (1) brain injury from bleeding or inadvertent trauma as a result of electrode insertion, (2) infection, (3) hardware failure, or (4) transient site-specific side effects related to overstimulation or unintentional stimulation of neighboring areas. The latter might produce diplopia, seizures, nausea, paresthesia, or headaches.

Overall, DBS surgery is a safe procedure with a relatively low risk of complications or unintended neurologic sequelae. However, data supporting its efficacy are limited. Currently, DBS for pain control is an extraordinary treatment that may be applicable to only a few chronic pain conditions. DBS implantable hardware is not approved by the FDA for pain control procedures, and many insurance carriers do not authorize implantation. Given the tremendous interest in and application of DBS for movement disorders, whether DBS for pain will be substantially resurrected at some point remains to be seen.

Motor Cortex Stimulation

In 1954, Penfield and Jasper observed that stimulation of the precentral (motor) gyrus elicited sensory responses when the corresponding portion of the adjacent postcentral gyrus had previously been resected.[73] They treated burning pain on one side of the body by postcentral gyrectomy, and when the pain recurred, they performed precentral gyrectomy, which then controlled the pain. In 1955 White and Sweet attempted surgical resection of the postcentral gyrus for relief of central pain and reported 13% pain relief.[74] It was not until 1971, after the publication of the gate theory in 1965, that Lende et al. re-explored the motor cortex as a potential site for pain control. In an attempt to treat central neuropathic facial pain,[75] they performed two cases of precentral and postcentral gyrectomy of the facial cortex. These reports formed the basis for establishing a link between the precentral and postcentral areas and pain control surgery.

By the 1980s the cumulative failure of other procedures, both modulatory and destructive, to fundamentally alter neuropathic pain made it clear that the development of an innovative methodology to surgically treat pain was critically needed. Exploration of the motor area as a target site is under way. Hardy et al. stimulated the rat medial prefrontal cortex with a resultant significant elevation in nociceptive response latency.[76,77] Hosobushi implanted electrodes in subcortical somatosensory areas for control of dysesthetic pain, and from this study, it was concluded that somatosensory stimulation could be effective in the treatment of leg pain.[78] In 1991 Tsubokawa et al. first introduced epidural stimulation of the motor cortex as an option to treat central deafferentation pain. His group had tried postcentral gyrus (sensory) stimulation and found that it was either ineffective or exacerbated the pain. They demonstrated that epidural MCS inhibited abnormal thalamic neuronal burst activity and increased regional blood flow to the cortex and thalamus.[79] Primarily, Tsubokawa et al. used MCS for central deafferentation pain syndromes, such as post-stroke pain.[79,80] The mechanism of action of MCS is still poorly understood. However, the work of Garcia-Larrea, Peyron, and coworkers[81–83] has shed some light on its mechanism of action. Positron emission tomography and electrophysiologic studies have demonstrated that MCS increases blood flow to the ipsilateral thalamus, cingulate gyrus, orbitofrontal cortex, insula, and brainstem, with some correlation between increased thalamic and brainstem blood flow and efficacy of pain relief. The increased blood flow to the ipsilateral sensory thalamus was greater than that to the motor (ventrolateral) thalamus. It does not appear that an intact somatosensory system is absolutely necessary for the clinical benefits to be realized, an important discovery allowing the use of this technology for stroke and other deafferentation states.[81–83] As with many forms of chronic stimulation, habituation seems to occur, which is more likely with the use of high frequency stimulation. The patient selection process for MCS is of paramount importance (as it is for all pain-relieving surgeries), and in this case, the debate continues. Neuropathic pain is more responsive to this form of therapy than nociceptive pain. Attempting to predict the best candidates for MCS can be challenging, and Yamamoto et al. introduced a pharmacologic classification of post-stroke patients based on their pain relief response to escalating doses of intravenous thiamylal and morphine. They concluded that patients with a good response to thiamylal or ketamine and a poor response to morphine were the best candidates for MCS.[84] Several neurogenic pain syndromes have been treated by MCS, including thalamic pain, bulbar post-stroke pain (which typically occurs with "Wallenberg's syndrome"), facial neuropathic and deafferentation pain, and phantom and brachial plexus avulsion pain.[85,86] Treatment of central post-stroke pain following thalamic infarction or thalamic or putaminal bleeding

by MCS was reported by Tsubokawa et al. to achieve good to excellent pain control in 65% of cases (follow up >12 months), with no seizures observed.[79,80] Katayama and associates extended the indications to include bulbar pain secondary to "Wallenberg's syndrome" and reported on four patients initially treated by VPL thalamic stimulation that resulted in increased pain. Three other patients were later treated by MCS, with a greater than 60% reduction in pain in two patients and greater than 40% in one patient.[87] Treatment of neuropathic facial pain appears to be one of the most promising indications for MCS, which may be related to the breadth of facial representation over the motor cortex. Several reports have described neuropathic facial pain treatment using MCS. Raslan et al. all treated trigeminal neuropathic pain with MCS and reported pain relief in approximately 60% of patients for up to 12 months.[86,88–93] Peripheral deafferentation pain and brachial plexus avulsion pain have also been treated by MCS, with variable results. Movement disorders are an active area of ongoing MCS research.[85] MCS has been shown to improve the symptoms of thalamic hand syndrome, action tremors, intention myoclonus, and Parkinson's disease.

MCS involves the implantation of epidural electrodes over the motor cortex (Fig. 32.1), which can be localized by (1) radiologic landmarks of the central sulcus, (2) intraoperative somatosensory evoked potentials with an observation of "phase reversal" over the central sulcus, (3) intraoperative stimulation of the cortex with concurrent electromyographic monitoring of the relevant muscle groups contralaterally, and, more recently, (4) the use of neuronavigation systems to localize either the central sulcus or the precentral gyrus. Some authors even recommend the use of functional magnetic resonance imaging for targeting, especially with infarctions involving the motor cortex.[94] A trial period of MCS is usually required, followed by implantation of a permanent system if the trial produces adequate relief. Complications of MCS include intraoperative seizures, stimulator pocket infection, epidural bleeding, subdural effusion, and "tolerance" to stimulation with diminished analgesia over time.

Unfortunately, long-term studies with extended follow up have shown poor chances of meaningful and sustained pain relief outcomes.[86,95] Therefore the procedure is rarely covered by insurance and is not commonly performed in the United States.

Spinal Cord Stimulation (SCS)

Approved by the FDA in 1989 as part of the treatment paradigm for chronic pain, SCS represents a safe and effective therapy, particularly for neuropathic pain. Indications include neuropathic pain with a spinal origin, CRPS, peripheral neuropathic pain, and anginal pain. Evidence for this has been borne out via randomized controlled trials and systematic reviews.[96–98]

Patients undergo a trial period of stimulation in which a percutaneous lead is placed into the extradural space. Stimulation was performed using an external generator. Typically, following a trial period of three to seven days, it is determined whether the trial is deemed successful based on the patient's perception of satisfactory pain relief. The trial lead is then removed, and the patient may undergo permanent implantation surgery.

Most commonly, these systems focus on the stimulation delivery of paresthesia-inducing frequencies. More recent research has focused on the investigation of novel waveforms including 10,000 Hz high frequency stimulation and "burst stimulation."[99–102] Randomized control trials have shown mixed results of the superiority of these novel waveforms.[102,103] Most recently, the concept of "closed loop" SCS has come to the forefront. This treatment paradigm uses feedback via a sensing arm to extract an actionable biomarker signal (evoked compound action potentials) that allows the device to self-adjust with the potential to maximize therapeutic efficacy.[104] This technology will need to be evaluated over time with well-designed outcome studies.

Dorsal Root Ganglion (DRG) Stimulation

Stimulation of the DRG is an alternative form of neuromodulation that is most effective for the treatment of CRPS type 2. This was evidenced by the pivotal FDA trial revealing DRG stimulation to be superior to SCS.[104] The procedure involves the placement of the epidural stimulator into the neuroforamen adjacent to the DRG. Similar to most neuromodulatory interventions, a trial period of stimulation is utilized as a confirmatory test prior to permanent implantation.

Peripheral Nerve Stimulation (PNS)

There is sparse evidence for the use of the peripheral nervous system, dependent on the nerve of interest that is being stimulated. In general, this intervention involves the placement of a stimulating electrode near the nerve. Similar to other neuromodulation procedures, a successful stimulation trial must precede permanent implantation. Recent recommendations have been produced by the Congress of Neurological Surgeons surrounding the deployment of occipital nerve stimulation (ONS).[105] Additionally, studies have explored the use of occipital nerve stimulation for trigeminal neuropathic pain.[106,107] Presently, nerve stimulators are being placed in the femoral and sciatic nerves for post-amputation pain and in the tibial nerve for foot pain.

The topics of SCS, DRG stimulation, and PNS are discussed in detail in Chapter 71.

Pharmacologic Neuromodulation

Intraventricular Opioids

Studies showing the direct analgesic effects of opioids applied in the ventricular region and around the medulla of the central nervous system[108,109] led to the work of Leavens et al. in 1982, in which human ICV use of morphine was first reported.[110] The profound analgesic response to intrathecal morphine coupled with its widespread clinical use for lower body pain suggested the need for more rostral injection sites to control pain in the head, neck, and upper extremity regions. Although cervical intrathecal opioid injection sometimes results in respiratory depression, it is possible to deliver a small amount of ICV morphine without respiratory dysfunction or dysautonomia. Opioid receptors are abundant around the wall of the third ventricle and aqueduct, as well as in the PVG and PAG. In Leavens et al.'s 1982 report, 1 mg of morphine was used to treat patients with intractable cancer pain, resulting in profound analgesia and no respiratory depression or neurologic changes.[110] In a report on 82 patients, Lazorthes and associates recommended nine specific guidelines for the ICV use of morphine: (1) chronic pain secondary to inoperable malignant tumors in patients with terminal cancer, (2) pain not relieved by medical treatment and, in particular, the development of serious side effects from using oral or systemic morphine, (3) intractable bilateral, midline, or diffuse pain not appropriate for percutaneous or open surgical interruption of nociceptive pathways, (4) chronic pain of somatic nociceptive origin (neurogenic pain was a contraindication), (5) upper body pain secondary to cervicothoracic cancer, (6) chronic pain of the lower half of

the body (subdiaphragmatic) only after failure of or contraindication to conventional intrathecal spinal opioid administration, (7) absence of general risks for complications, such as coagulation disturbances, cutaneous infection, and septicemia, (8) informed consent from the patient and family, and (9) the presence of a favorable domestic environment (e.g. physician, nurse, or family) for ambulatory surveillance and chronic ICV morphine treatment. The authors recommended that when the topography of the pain involved a transitional area (e.g. lower thoracic, diaphragmatic, or upper abdominal region), ICV morphine could be indicated if the patient fails a more standard intrathecal morphine trial.[111]

Surgically, the implantation of a chronic ICV morphine infusion system involves placement of a catheter into the lateral ventricle near the foramen of Monro to deliver drugs near target receptors in the periaqueductal parenchyma of the midbrain (Fig. 32.1). The analgesic latency of ICV morphine administration was between 15 and 30 min, and the effect lasted for a mean of 28 h. Excellent or good pain relief rates range from greater than 50% to 97%, and side effects include somnolence, nausea, confusion, and respiratory depression, which are usually transient. Finally, Lazorthes et al. reported tolerance in three of 82 patients.[111]

The increased effectiveness of oral opioids has diminished the need for ICV morphine administration. However, the technique remains relatively simple and effective and is a viable option for patients with intractable pain of malignant etiology, following oral opioid failure and when pain is diffuse or cephalic in topography.[112]

Intrathecal Opioids

The main advantage of intrathecal opioid administration is the ability to achieve therapeutic efficacy via a smaller dose without the side effects induced by peripheral administration.[113,114] Similar to neuromodulation, patients undergo a trial prior to proceeding with a permanent implant. This approach involves accessing the intrathecal space via the lumbar cistern and advancing an intrathecal catheter up to the mid-thoracic spine. The catheter is then connected to a programmable pump with a reservoir that was placed in the abdominal adipose layer. The reservoir requires scheduled refills of medication, the frequency of which is determined by the patient's infusion rate, medication concentration, and reservoir capacity.[115]

Beyond opioids, multiple medications have been used by providers to treat chronic pain via the intrathecal route. These medications include clonidine, ziconotide, benzodiazepines, and tricyclic anti-depressants, among others.[116] The most commonly used drugs are clonidine and ziconotide. The potential advantage of non-opioid medications is the decrease in the potential for unwanted side effects, development of dependency, and risk of medication withdrawal in the event of a pump failure.[117] Intrathecal therapies are further discussed in Chapter 72.

Summary

Neurosurgical procedures to treat intractable pain have gone through an evolutionary process, dictated in part by technologic advances, scientific discovery, and changes in the survival rates of patients with chronic pain, especially those with cancer pain. Irreversible ablative procedures are used much less frequently today, yet they remain the procedures of choice on occasion. Depending on the physiologic substrate and pain topography, multiple brain and spinal cord regions can be targeted to treat chronic pain. Neuromodulation by either electrical stimulation or pharmacologic manipulation is generally the preferred approach to treat chronic pain.

Key Points

- Neurosurgical treatments for intractable pain are usually reserved as the last option for the treatment of intractable pain.
- These interventions can be either ablative or neuromodulatory, which can be divided into pharmacologic and electrical.
- Neurosurgical procedures can be performed at either the spinal or cerebral level. Spinal spinothalamic ablation (cordotomy) is the most studied and performed neurosurgical ablative procedure, and it is very effective in treating unilateral somatic cancer pain.
- Opioid use has limited the indications for ablative procedures, but there are still defined but limited indications for spinal ablative procedures that are confined to cancer-related pain.
- Spinal neuromodulation (i.e. SCS and intrathecal opioid devices) is widely used to treat chronic spinal pain.
- Advances in spinal cord stimulation include high frequency and burst stimulation and "closed loop" SCS.
- PNS involves the placement of the electrode near the nerve. Studies have shown a beneficial effect of occipital nerve stimulation. Clinically, electrodes are placed in the femoral and sciatic nerves for post-amputation pain and in the tibial nerve for foot pain.
- Clinical intrathecal therapies involve mainly opioids, ziconotide, and baclofen.
- Cerebral ablation of pain pathways or centers is rarely performed. However, cerebral neuromodulation procedures, such as deep brain stimulation and motor cortex stimulation, may have limited indications and utility that are usually related to central pain and neuropathic pain.

Acknowledgment

The authors thank Shirley McCartney, Ph.D., for her editorial assistance.

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33

Evaluation and Treatment of Cancer-Related Pain

DERMOT FITZGIBBON, MARGARET HSU

Introduction

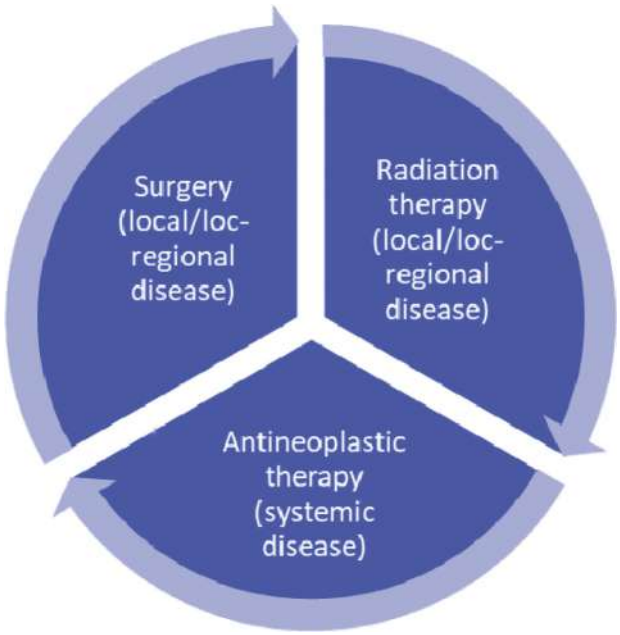
Cancer is a disease process that results when cellular changes cause uncontrolled growth and division of cells. It continues to be a major health problem and is the second leading cause of death in the United States.[1] The three most prevalent cancers in 2019 were prostate, colon, and rectum, and melanoma of the skin among males, and breast, uterine corpus, and colon and rectum among females.[2] Common side effects of cancer and its treatment are pain, fatigue, and emotional distress,[3,4] all of which can affect functional status. Pain can be problematic at different phases of cancer treatment. Van den Beuken-van Everdingen et al.[5] reported pain prevalence rates of 39% after curative treatment; 55% during anticancer treatment; 66% in advanced, metastatic, or terminal disease; and 51% in all cancer stages. There was a prevalence rate of 38% of moderate to severe pain in studies reporting pain intensity. Hematologic patients also have high prevalence rates of pain at diagnosis, during therapy, and in the last month of life.[6] Despite the availability of opioids and other treatment strategies, undertreatment of cancer pain remains problematic,[7,8] with some authors estimating that one in three patients does not receive an analgesic prescription to match the reported level of pain.[9] Despite increased attention to cancer pain, pain prevalence in cancer patients has not significantly changed over the last decade compared to the prior four decades.[10] This continues into survivorship, where the prevalence of pain also is high.[11] At initial diagnosis, oncology patients face a continuum of care that may progress from disease-oriented, curative, life-prolonging treatment through symptom-oriented, supportive, and palliative care extending to terminal-phase hospice care (Fig. 33.1).

Treatments are usually multifaceted and often include surgery, radiation therapy, and systemic treatment, which includes the use of chemotherapeutic cytostatic drugs, targeted therapy with small molecule inhibitors, monoclonal antibodies that involved targeted immunotherapy, and inhibition of tumor-associated angiogenesis or immune regulation by checkpoint inhibitors (Fig. 33.2, Table 33.1).

Once treatment is completed, patients frequently require an extended interval of surveillance, resulting in additional treatments for recurrences or the appearance of new diseases or problems. Advances in cancer prevention and treatment with an improved understanding of the biology of cancer have resulted in improved patient survival and quality of life.[12] Cancer survival has improved since the mid-1970s for all of the most common cancers except uterine cervix and uterine corpus,[13] and there has been an overall drop of 29% in the mortality rate since 1991.[1] Even after completion of care, pain can be a persistent problem, and the ability to address this is an increasing issue because of advances in cancer treatment with a record number of survivors in the United States.[12] Pain management should be an integral component of the cancer care continuum. For oncology patients, the ultimate goal is to cure disease and pain, often an undesirable consequence of disease or treatment. Although pain management should be integrated into oncology care, it should not be the focus of care in contrast to many chronic pain models. Interdisciplinary collaboration is essential for the comprehensive care of cancer patients with pain. Aggressive therapy of both cancer and pain is mutually beneficial and is best done by skilled, interdisciplinary teams that understand and respond to the changing demands of oncology care that include pain management.

The most successful strategy for managing tumor-related pain is identifying the source and directing appropriate anti-tumor measures (which may include all care options in oncology) toward the source. Symptomatic management of the pain may be appropriate while implementing these measures. However, such measures may not be appropriate for patients with pre-existing chronic non-cancer-related pain who present for oncology care. These issues can usually be differentiated by a comprehensive pain assessment with a clear understanding of the current tumor location(s) and correlation with the patient's pain complaint. The goal of any pain management strategy is to manage pain that allows for the optimization of function and enable an acceptable quality of life. Although a reduction in pain intensity is ideal, the guiding principle for pain management should be an improvement in function. Adequate management of cancer pain depends on making an accurate diagnosis of the underlying cause(s) of pain and contributing factors. In every situation, this requires a comprehensive assessment of these issues. The diagnosis will include a reason for the pain complaint, a summary of the current disease status, the appropriateness and efficacy of the current pain medication regimen, and an assessment of functional and social status. It is important to recognize that the source of pain in the cancer patient is usually not a single entity but often has multiple sources that may result from different issues such as tumor staging, treatment phase, preexisting conditions causing chronic pain, and posttreatment complications. Tumor-related pain may be classified according to the tissue source as nociceptive (somatic or visceral) or neuropathic. Once a treatment plan is implemented,

• **Figure 33.1** Cancer Care Continuum.



• **Figure 33.2** Major modalities of cancer therapy.

assessment and re-assessment at regular intervals are key to ensuring that treatment is appropriate and safe, as well as minimizing and addressing side effects related to treatment throughout care. The concurrent use of adjunctive, specialized, or complementary therapies should be considered, and referral for specialized surgical, anesthetic, or psychological intervention benefits selective patients. However, most patients can attain adequate management of pain (and improvement in function) using appropriate oral pharmacotherapy. Cancer (tumor-related) pain management guidelines typically incorporate pharmacologic, anesthetic, neurosurgical, and behavioral approaches. The mainstay of cancer pain therapy is pharmacologic, but radiotherapeutic, anesthetic, neurosurgical, psychological, physiotherapeutic, spiritual, and social interventions all play roles in adequate cancer pain management (Table 33.2). The basic principles of tumor-directed pain control include modifying the source of pain by treating cancer, altering the central perception of pain (for example, by the use of analgesics, anti-depressants, anxiolytics, and psychotherapy), and, when appropriate, interfering with nociceptive transmission outside of and within the central nervous system, for example, with anesthetic techniques (e.g. neurolytic celiac plexus block, neuraxial analgesia, and spinal neurolysis), or neurosurgery procedures (e.g. cordotomy, dorsal root entry zone lesioning). Options for disease modification should always be foremost.

World Health Organization Analgesic Ladder

In 1986, the World Health Organization (WHO) developed a simple model for the introduction and upward titration of analgesics, which became known as the WHO analgesic ladder.[14] In 2018, WHO updated its guidelines for pharmacologic and radiotherapeutic management of cancer pain (WHO 2018). Pharmacologic options should be used by following the WHO analgesic ladder (Fig. 33.3).

Implementation of the three-step ladder, in combination with appropriate dosage guidelines, should result in adequate pain relief for 70%–90% of patients.[15–17] Successful implementation of the ladder requires adherence to basic principles of medication use (Table 33.3).

The ladder advocates for the use of analgesics (non-opioids including automatic positive airway pressure [APAP] and non-steroidal anti-inflammatory drugs [NSAIDs], adjuvant analgesics such as anti-depressants and anticonvulsants, and opioids) should be used incrementally according to pain intensity with the focus on the use of opioids for moderate to severe intensity pain. Opioids are commonly used to treat moderate or severe cancer pain, and the most commonly used opioid drugs are buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, tramadol, and tapentadol.[18] For initiation and maintenance of pain relief, NSAIDs, APAP, and opioids either alone or in combination may be used with a strength appropriate for patient-reported pain severity. The use of steroids for the shortest time possible is recommended if deemed appropriate for care, but evidence for the efficacy of steroids in cancer pain is weak, and the side effect profile of prolonged use needs to be defined.[19] Optimal dosing of steroids likely depends on location and type of pain, presence of or risk of infection, stage of illness, presence of diabetes mellitus, and goals of care. In patients with pain related to bone metastases, bisphosphonates or monoclonal antibodies (denosumab) should be considered to prevent and treat bone pain. Regarding the use of anti-depressants and

TABLE 33.1 Types of Cancer Treatment

Surgery	Open versus minimally invasive Primary tumor resection Resection of metastases Cytoreduction Palliative Reconstructive
Radiation Therapy	External beam (photon, proton, neutron)* Internal radiation therapy (brachytherapy) Systemic radiation therapy (radioactive iodine, radium, radiostrontium)
Chemotherapy	Cytotoxic (oral, IV, injection, intrathecal, intraperitoneal, intra-arterial)
Immunotherapy	Immune checkpoint inhibitors Cellular immunotherapy (CAR T-cell, TIL) Monoclonal antibodies (rituximab) Cancer treatment vaccines Immune system modulators (cytokines – interferons, interleukins; BCG; immunomodulatory drugs – thalidomide, lenalidomide, pomalidomide, which are also angiogenesis inhibitors)
Targeted Therapy	Tyrosine kinase inhibitors (e.g. erlotinib for EGFR, venetoclax for BCL2, imatinib for BCR-ABL mutations in CML, ibrutinib in CLL) Monoclonal antibody-drug conjugate (e.g. brentuximab-vedotin for lymphoma, obinutuzumab-ozogamicin for ALL) Angiogenesis inhibitors primarily target VEGF (e.g. bevacizumab, everolimus) Hormone therapy Gene therapy
Hormone Therapy	Oral Injection Surgery (oophorectomy, orchiectomy)
Stem Cell Transplant	Autologous Allogenic Syngeneic
Precision Medicine	Certain tumors, including melanoma, some leukemias, and breast, lung, colon, and rectal cancers, may be tested for certain genetic changes

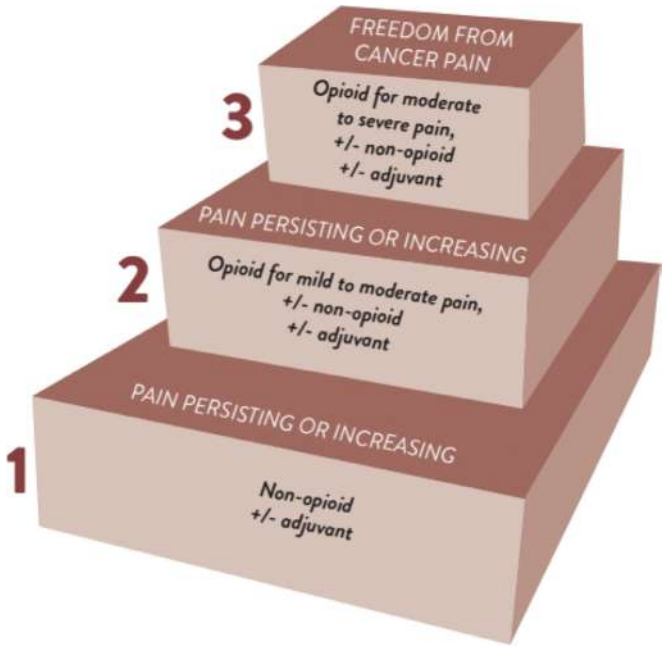
*Types of external beam radiation therapy include 3-D conformal therapy, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic radiosurgery, and stereotactic body radiation therapy.

ALL, Acute lymphoblastic leukemia; *BCG*, Bacillus Calmette- Guérin; *BCL2*, B-cell lymphoma 2; *BCR-ABL*, Breakpoint cluster region protein. The symbol ABL1 is derived from Abelson, the name of a leukemia virus. A fusion gene is created by juxtaposing the ABL1 gene on chromosome 9 (region q34) to a part of the BCR gene on chromosome 22 (region q11); *CAR-T*, chimeric antigen receptor; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myeloid leukemia; *EGFR*, epidermal growth factor receptor; *IV*, intravenous; *TIL*, tumor-infiltrating lymphocytes; *VEGF*, vascular endothelial growth factor.

TABLE 33.2 Approaches to Oncology Pain Management

Drugs	Analgesics (opioids, NSAIDs, APAP) Adjuvant analgesics (anti-depressants, anti-convulsants) Steroids
Psychosocial	Cognitive behavioral Stress management, including biofeedback Social support
Integrative medicine	Acupuncture Massage Hypnotherapy
Physical therapy and Rehabilitation	Flexibility, strength, endurance, aerobic conditioning Lymphedema control
Modification of pathologic process	Radiation therapy Chemotherapy Surgery
Interruption of pain pathways	Local anesthetics Neurolytics (alcohol, phenol) Thermal ablation (radiofrequency, cryoablation) Neurosurgery (cordotomy, DREZ, anterior cingulotomy)

APAP, Automatic positive airway pressure; *DREZ*,**; *NSAIDs*, nonsteroidal anti-inflammatory drugs.



• **Figure 33.3** World Health Organization analgesic ladder (2018).

TABLE 33.3 Principles of Analgesic Use

Principle	Comment
By mouth	Oral intake is preferred. Transdermal/transmucosal can also be considered.
By the clock	Give medications regularly. Anticipate pain problems, particularly breakthrough pain. For opioid use, schedule ATC opioids and use BTP opioids as needed.
For the individual	Patient responses vary by patient and by medication. Variations in drug metabolism may cause unpredictable pharmacokinetics.
With attention to detail	Regular assessment of response to a regimen is essential. Assume patients may not follow a new regimen accurately or as prescribed.

ATC, Around the clock; *BTP*, breakthrough pain.

anti-convulsants for cancer pain management, the WHO report did not make a recommendation for these classes of medications for the treatment of cancer-related neuropathic pain. Adequate data from clinical trials regarding the use of anti-depressants and anti-convulsants in oncology pain was not available. In the absence of clear evidence in favor of use, practitioners may consider an individual trial of therapy and prescribe for those patients without adequate pain relief or have severe/unmanageable side effects to standard analgesic regimens. Drugs or drug classes recommended for the management of neuropathic pain are listed in Table 33.4.

Acetaminophen

N-acetyl-p-aminophenol (APAP) is an antipyretic/analgesic drug that is discussed extensively in Chapter 49. Hepatotoxicity is the most well-known severe adverse effect of APAP. Particularly in cases of overdose, APAP characteristically shows direct hepatocellular injury.[20] Hepatocellular injury may result in elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) blood levels, usually 24–48 h after ingestion. Elevated ALT level greater than three times the upper limit of normal was seen in 33%–44% of normal volunteers who were administered 4 g of APAP daily for 14 days.[21] The maximum daily therapeutic dose of 3900–4000 mg was established in separate actions in 1977 and 1988, respectively, via the Food and Drug Administration (FDA) monograph process for nonprescription medications. The 3900 mg maximum daily dose, as recommended originally, was deemed to be safe and is five to seven times lower than the estimated median lethal dose (LD50) of 400 mg/kg.[22] Some studies have indicated that daily APAP doses of 4000 mg for 6 to 12 months demonstrated that no patient exceeded liver function tests beyond two times the upper limit of normal.[23] The FDA has conducted multiple advisory committee meetings to evaluate acetaminophen and its safety profile and has suggested (but not mandated) a reduction in the maximum daily dosage from 3900–4000 mg to 3000–3250 mg, which appears based on the potential of an overdose occurring if a patient was not using acetaminophen properly or if, unknowingly, a patient was using multiple acetaminophen-containing products. The concern was not with therapeutic dosing (≤4000 mg/24 h) but with excessive dosing when two or more products containing acetaminophen are taken inadvertently and the potential for hepatotoxicity with chronic use at excessive doses. In a Cochrane review, there was no high quality evidence to support or refute the use of APAP alone or in

TABLE 33.4 Drugs or Drug Classes With Strong or Weak Recommendations for the Management of Neuropathic Pain[192]

	Total Daily Dose and Dose Regimen	Recommendations
Strong Recommendations for Use		
Gabapentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin noradrenaline reuptake inhibitors duloxetine or venlafaxine[a]	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic anti-depressants	25–150 mg, once a day or in two divided doses	First line[b]
Weak Recommendations for Use		
Capsaicin 8% patches	One to four patches to the painful area for 30–60 min every three months	Second line (peripheral neuropathic pain)[c]
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)

[a]Duloxetine is the most studied, and therefore recommended, of the serotonin noradrenaline reuptake inhibitors.

[b]Tricyclic anti-depressants generally have similar efficacy; tertiary amine tricyclic anti-depressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side effects and potential risk of falls; an increased risk of sudden cardiac death has been reported with tricyclic anti-depressants at doses greater than 100 mg daily.

[c]The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibers, which might be a cause for concern in progressive neuropathy.

Reprinted with permission from Elsevier. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–173.

combination with opioids for the first two steps of the three-step WHO cancer pain ladder.[24] It was not clear whether any additional analgesic benefit of acetaminophen could be detected in the available studies. In an era of concern for opioid prescribing, there is a tendency to prescribe regular and higher doses of APAP (up to 4 G/day) in cancer patients. Toxicity from high daily doses of APAP is of concern. Unintentional fever suppression in patients receiving chemotherapy is also an issue. APAP should be used cautiously and not for extended periods in oncology patients receiving active treatment.

Nonsteroidal Anti-inflammatory Medications

NSAIDs exhibit their action by inhibiting the cyclooxygenase (COX) enzyme, which consists of two isoforms named as COX-1 and COX-2. Most NSAIDs are nonselective and inhibit both COX-1 and COX-2. Celecoxib is the only marketed drug belonging to the class of selective COX-2 inhibitors approved by the FDA. COX-2 overexpression is demonstrated throughout various steps of tumorigenesis to metastasis, and COX-2 expression directly co-related with increased prostaglandin levels in neoplastic tissues, particularly in the gastrointestinal tract,[25] and possibly breast.[26] Long-term use of (low dose) aspirin and non-selective NSAIDs are potential candidates for chemoprevention of gastrointestinal cancer.[27] The anti-inflammatory activity of NSAIDs in descending order is indomethacin > diclofenac > piroxicam > ketoprofen > lornoxicam > ibuprofen > ketorolac > acetylsalicylic acid. The greater the degree of COX-1 block, the greater the tendency to cause gastrointestinal (GI) ulceration and the promotion of bleeding. From the first day of use, all NSAIDs increase the risk of GI bleeding, myocardial infarction, and stroke. The risk of bleeding is low for patients using NSAIDs intermittently. NSAIDs increase the risk of GI bleeding by inhibiting platelet aggregation, causing gastric mucosa lesions, ulceration, overt bleeding, enteropathy, and occult bleeding associated with a decrease in hemoglobin. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for three to six months and in about 2%–4% of patients treated for one year. Even short-term (zero to three days) treatment with NSAIDs was associated with increased risk of bleeding compared with no NSAID use in patients receiving antithrombotic therapy.[28] Non-selective NSAIDs increase the risk of a GI bleed four fold, whereas COX-2 inhibitors increase this risk three fold. Co-prescription of NSAIDs with corticosteroids increases bleeding risk 12-fold, spironolactone 11-fold, and SSRIs 7-fold.[29] Monotherapy with non-selective NSAIDs increased the risk of upper GI bleeding by an incidence rate ratio (IRR) of 4.3 to a greater extent than monotherapy with COX-2 inhibitors (IRR, 2.9) or low-dose aspirin (IRR, 3.1). Combination therapy generally increased the risk of GI bleeding; concomitant NSAID and corticosteroid therapies increased the IRR to the greatest extent (12.8) and produced the greatest excess risk relative excess risk because of an interaction (RERI of 5.5. Concomitant use of NSAIDs and aldosterone antagonists produced an IRR for upper GI bleeding of 11.0 (RERI 4.5). The excess risk from the concomitant use of NSAIDs with selective serotonin reuptake inhibitors (SSRIs) was 1.6, whereas that from the use of COX-2 inhibitors with SSRIs was 1.9, and that for the use of low-dose aspirin with SSRIs was 0.5. Excess risk of concomitant use of NSAIDs with anticoagulants was 2.4, of COX-2 inhibitors with anticoagulants was 0.1, and of low-dose aspirin with anticoagulants was 1.9.[29] Concomitant use of non-selective NSAIDs or low dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces a significant excess risk of upper GI bleeding. Castellsague et al. pooled relative risks (RRs) of upper GI complications associated with individual NSAID use.[30] Agents such as celecoxib and ibuprofen have a low RR (1.5 and 1.8, respectively), while piroxicam and ketorolac have a higher RR (7.4 and 11.5, respectively).

Approximately 10% of the total drug-induced hepatotoxicity is NSAID-related.[31] Sulindac and diclofenac are the NSAIDs most associated with hepatotoxicity, but virtually all NSAIDs have been linked to at least rare cases of clinically apparent drug-induced liver injury. The most common adverse effects affect the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system. The mechanism of injury to the liver is usually hepatocellular, but cholestatic injury can also occur.[32] COX-2 selective inhibitors and non-selective NSAIDs are associated with an increased risk of acute cardiovascular events.[33] Even one week of NSAID use is associated with an elevated risk of myocardial infarction (MI), and this phenomenon may apply to those with no prior history of MI. While the risk increases with increasing dosage, the risk appears to plateau after a one-month duration of use.[34] In older patients with arthritis and established coronary artery disease or risk factors who used chronic NSAID therapy (celecoxib 100–200 mg twice daily, ibuprofen 600–800 mg thrice daily, or naproxen 375–500 mg twice daily), naproxen and ibuprofen at moderate doses were associated with more cardiovascular events that with celecoxib.[35] The vascular risks of high-dose diclofenac (150 mg/day) and possibly ibuprofen (2400 mg/day) are comparable to coxibs. In contrast, high-dose naproxen (1000 mg/day) is associated with less vascular risk than other NSAIDs.[36] NSAIDs can cause serious renal adverse effects, which include sodium and water retention with edema, worsening of heart failure, hypertension, hyponatremia, hyperkalemia, acute kidney injury, renal papillary necrosis, and acute interstitial nephritis. Acute forms of kidney injuries are transient and often reversible upon drug withdrawal. Approximately 1%–8% of patients taking NSAIDs develop renal adverse effects such as a reduction in glomerular filtration rate, acute renal failure, renal papillary necrosis, nephrotic syndrome, acute interstitial nephritis, and chronic renal failure.[37] NSAIDs, unlike aspirin, bind reversibly at the active site of COX-1, usually depressing platelet thromboxane formation to the degree that platelet function is impaired for only a portion of the dosing interval. Platelet function normalizes within 24 h of the last dose of ibuprofen in healthy volunteers who took 600 mg q 8 h for one week.[38]

Studies on the use of NSAIDs in cancer (including both aspirin and non-aspirin NSAIDs) show inconsistent and contradictory findings in terms of the role of these drugs in cancer, with some reporting an increased risk in certain types of cancer and others showing a reduction in cancer risk.[39] Although many NSAIDs are available to treat various painful conditions, it is unclear which agent is most clinically efficacious for relieving cancer-related pain and if there are clinical differences between these agents that justify their cost differences. In a Cochrane review of the use of NSAIDs either alone or in combination with opioids, the quality of evidence supporting the use of NSAIDs was poor and suggested that moderate to severe cancer pain was reduced to no worse than mild pain after one to two weeks in approximately 1:3 patients. One in four patients stopped taking NSAIDs because the drug did not work, and 1:20 stopped because of side effects.[40] In effect, there is no evidence to support or refute the use of NSAIDs alone

or in combination with opioids for cancer pain.[40,41] The long-term use of NSAIDs for pain management is not advisable in patients with cancer, particularly because of the additional bleeding risks in cancer patients undergoing active treatment with myelosuppressive regimens and the probability that a patient with cancer may be on a broad regimen of medications, some of which may increase NSAID-related toxicity (myocardial infarction, gastrointestinal bleeding, and renal failure).

Antiepileptic Drugs

The pharmacologic mechanism of action responsible for therapeutic effects in pain management is unclear (Table 33.5) and may involve enhancement of GABAergic inhibition, decreased glutamatergic excitation, modulation of voltage-gated sodium and calcium channels, and effects on intracellular signaling pathways.[42]

Antiepileptic drugs (AEDs) are often administered as polytherapy or combined with other treatments. The pharmacokinetics of carbamazepine is nonlinear because of autoinduction that completes within three weeks and can result in a threefold increase in elimination. It is extensively metabolized in the liver, primarily by CYP3A4. Because of this, it is readily inducible and potently inhibited. Therefore it is subject to many pharmacokinetic drug-drug interactions. As well as being an enzyme-inducing drug, carbamazepine is affected by the autoinduction of CYP3A4-mediated metabolism. This mainly occurs at the beginning of treatment when clearance can increase up to three times during the first two to three weeks. Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin may reduce the levels of cyclosporin, tacrolimus, and corticosteroids, delaying the immunosuppressant effect by up to ten days.[43] Gabapentin, lacosamide, levetiracetam, pregabalin, and vigabatrin are essentially not associated with clinically significant pharmacokinetic interactions.[44]

Gabapentinoids include gabapentin and pregabalin. The α2δ-1, commonly known as a voltage-activated Ca2+ channel subunit, is a binding site of gabapentinoids.[45] Gabapentinoids commonly

TABLE 33.5 Antiepileptic Drugs

Medication	Mechanism of Action	Indication	IR	ER	Comment
Valproate	Influences GABAergic neurotransmission. It is also thought to block sodium and calcium channels.	Epilepsy, acute mania/ bipolar disorder, and migraine prophylaxis.	Yes	DR and ER tablets	ER formulation has lower bioavailability. Doses need to be increased by 12% (8%–20%) compared to the standard formulation. Effective for migraine prevention. Risk of fetal malformation. Adverse benefits include liver function test abnormalities, dizziness, drowsiness, and nausea. Maximum dose is 60 mg/kg/day.
Carbamazepine	Blocks voltage-gated sodium channels.	Epilepsy (especially partial seizures), bipolar disorder, and trigeminal neuralgia.	Yes	Carbatrol or Tegretol-XR	Side effects include hyponatremia, leukocytosis, thrombocytopenia, dizziness, drowsiness, ataxia, nausea/vomiting, and blurred vision. Dosing starts at 100–200 mg twice a day and is titrated up by 200 mg/day every three to five days until pain relief is achieved. The maximum dose is 1200 mg/day.
Phenytoin		Partial and generalized seizures; monotherapy for trigeminal neuralgia.	Yes	ER	Non-linear pharmacokinetics.
Oxcarbazepine	Blocks voltage-gated sodium channels.	Focal seizures with or without secondary generalization.	Yes	ER	ER peak concentrations are 19% lower than with OXC IR. It can be started at 300 mg twice a day and titrated up by 300 mg/day every three days for therapeutic effect. The maximum dose is 2400 mg/day.
Lamotrigine	Blocks Na+ channels, neuronal α-4-β2-nicotinic acetylcholine receptors may be a target.	Partial seizures, the generalized seizures of Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures. Mood stabilizer in bipolar.	Yes	XR	Risk of Stevens-Johnson. Start at low doses (25 mg/day) with weekly titration to target dose. Syndrome, blood dyscrasia.

TABLE 33.5 Antiepileptic Drugs—cont'd

Medication	Mechanism of Action	Indication	IR	ER	Comment
Lacosamide	Selectively enhances the slow inactivation of voltage-gated sodium channels and interacts with the collapsin-response mediator protein-2.	Primary generalized tonic-clonic seizures, partial onset seizures.			Dosing starts at 50 mg twice daily and can be increased to 400 mg/day. Abrupt discontinuation can precipitate seizures. No convincing evidence of efficacy in neuropathic pain and fibromyalgia at doses of 200–400 mg daily.
Gabapentin	Binds to calcium channels and modulating calcium influx. Exert analgesic effect through high affinity binding and modulation of the calcium channel α2-δ proteins in the dorsal root ganglion.	Partial seizures, postherpetic neuralgia.	Yes	ER	Compared with other anti-convulsant drugs, the α2-δ ligands do not have significant drug interactions, predominantly because of their lack of hepatic metabolism or their modulation of cytochrome P450 activity. Nonlinear pharmacokinetics (absorbed in the proximal small bowel by the L-amino acid transporter, which is a saturable mechanism).
Pregabalin	Binds to calcium channels and modulating calcium influx. Exert analgesic effect through high affinity binding and modulation of the calcium channel α2-δ proteins in the dorsal root ganglion.	Painful diabetic peripheral neuropathy, postherpetic neuralgia, partial onset seizures, fibromyalgia, neuropathic pain associated with spinal cord injury.	Yes	ER	Compared with other anti-convulsant drugs, the α2-δ ligands do not have significant drug interactions, predominantly because of their lack of hepatic metabolism or their modulation of cytochrome P450 activity. Unlike gabapentin, it has linear pharmacokinetics over its recommended dose ranges. Start at low doses (50 mg daily), adding 50 mg each week on a twice a day basis to a max of 600 mg per day.
Topiramate	Blocks activity-dependent, voltage-gated sodium channels; enhance the action of GABA receptors; inhibit L-type voltage-gated calcium channels; presynaptically reduce glutamate release, and postsynaptically block kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.	Generalized tonic-clonic seizures, partial seizures, migraine.	Yes	ER	Dosing starts at 50 mg/day and can be titrated up to 400 mg/day. No convincing evidence of efficacy in neuropathic pain. Serious adverse events thought to be related to topiramate included convulsion and bradycardia plus syncope. Additional adverse effects include sedation, nausea, diarrhea, and metabolic acidosis.

IR = Immediate release.
ER/XR = Extended release.
DR = Delayed release.

cause adverse effects such as sedation, confusion, dizziness, ataxia, visual disturbances, and altered cognition. Combined with opioids, this side effect profile can be potentiated. For first-time pregabalin users, dizziness and somnolence were reported by 25% and 14% of patients, respectively.[45] Gabapentinoids have the potential to be abused with an estimated prevalence of 1.6% in the general population with ranges from 3% to 68% among opioid abusers,[46] and are associated with euphoria, sedation, and dissociation. Gabapentin was misused primarily for recreational purposes, self-medication, or intentional self-harm and was misused alone or combined with other substances, especially opioids, benzodiazepines, and/or alcohol.[47] Risk factors for abuse include a history of substance abuse, particularly opioids, and psychiatric comorbidities. Sedation and dizziness are relatively common, and some patients experience cognitive difficulties while taking these drugs.[48] In 2008, the FDA issued a warning on all AEDs that these drugs have an increased risk of suicidal thoughts and behaviors. The relative risk was higher in the epilepsy patient group when compared to the groups of patients receiving AEDs for psychiatric and other conditions. However, patients and clinicians should not avoid the use of AEDs because of the risk of suicidality.[49] However, the high prevalence of comorbid behavioral health issues in patients treated with AEDs suggests that the association is confounded by indication, preexisting mental health conditions, and medications received. In a cohort analysis,

Patorno et al.[50] found an increased risk for these events in new users of gabapentin, lamotrigine, oxcarbazepine, and tiagabine compared with topiramate. A secondary analysis confirmed the increased risk and identified an excess of 5.6 cases of attempted or completed suicide per 1000 person-years among new users of gabapentin, 10.0 cases per 1000 person-years among new users of oxcarbazepine, and 14.1 cases per 1000 person-years among new users of tiagabine compared with topiramate. The risk remained increased for gabapentin in subgroups of younger and older patients, patients with a mood disorder, and patients with epilepsy or seizure disorders.

Gabapentinoids are indicated for the treatment of epilepsy, peripheral and neuropathic pain, fibromyalgia, and generalized anxiety disorder in adults. Recommendations for use and doses in neuropathic pain are listed in Table 33.4. For gabapentin, the only pain related indication approved by the FDA is postherpetic neuralgia. For pregabalin, FDA-approved indications related to pain are limited to postherpetic neuralgia, neuropathic pain associated with diabetic neuropathy or spinal cord injury, and fibromyalgia. Despite these limited indications, gabapentin and pregabalin are widely prescribed off-label for multiple different pain complaints.[51] A common mistaken perception is that an effective drug for one type of neuropathic pain is beneficial for all neuropathic pain, regardless of underlying etiology or mechanism. Recommendations across guidelines consistently endorse gabapentinoids as first line agents for general neuropathic pain complaints but that the overall quality of these guidelines is poor.[52] Similarly, the evidence does not support gabapentinoid therapy for low back pain or radiculopathy, suggesting that pregabalin was ineffective.[53] A Cochrane review showed that some patients with neuropathic pain would benefit substantially from pregabalin, while more are having moderate benefit, and many are without any benefit.[54] Gabapentin can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy, but evidence for other types of neuropathic pain is very limited.[55,56] Similarly, there is little evidence to support the effectiveness of oxcarbazepine in painful diabetic neuropathy, neuropathic pain from radiculopathy, and a mixture of neuropathies.[56] Overall, there is low quality evidence that gabapentinoids are effective in reducing pain intensity in patients with cancer pain.[57]

Anti-depressants

Anti-depressants can be classified into different classes based on their mechanisms of action (Table 33.6).

The two classic mechanisms are demonstrated by tricyclic antidepressants and monoamine oxidase inhibitors. The nonclassical anti-depressants, the most widely prescribed agents, are SSRIs and dual serotonin norepinephrine reuptake inhibition (SNRI). Anti-depressants have virtually no antinociceptive effects but are prescribed for neuropathic pain. Tricyclic anti-depressants and serotonin noradrenaline reuptake inhibitors are used to treat chronic pain, such as neuropathic pain and fibromyalgia. SSRIs are generally the first line anti-depressants for the treatment of depression in cancer patients because of their tolerability profile. SSRIs, which are frequently used to treat depression, are not effective against chronic pain.[58] The inhibitory effects of anti-depressants for neuropathic pain manifest more quickly than their anti-depressant effects, suggesting different modes of action. The analgesic effect on chronic pain may manifest in as little as a few days to one week, whereas the anti-depressant effects may take two to four weeks.[59] Anti-depressants that inhibit the reuptake of both noradrenaline and 5-HT have stronger analgesic effects than a drug that selectively inhibits the reuptake of only one of these neurotransmitters, and norepinephrine plays a greater role than 5-HT in the analgesic action. Anti-depressants have several other actions in addition to increasing monoamines that may contribute to the inhibition of neuropathic pain, such as sodium channel blockers, *N*-methyl-D-aspartate (NMDA) receptor antagonists, effects on α-1 receptors, calcium channel blockers, potassium channel activators, modulation of the adenosine system, and activation of GABA-B receptors.[59] Serotonin and dopamine may reinforce the noradrenergic effects to inhibit neuropathic pain. Increasing norepinephrine in the spinal cord by reuptake inhibition directly inhibits neuropathic pain through α2-adrenergic receptors. Also, increasing norepinephrine acts on the locus coeruleus and is an essential element of both the ascending and descending pain modulator systems regulated by these anti-depressants.[60] TCAs (amitriptyline, nortriptyline, and desipramine) have been the first line treatment for neuropathic pain for many years, but only a minority of people will achieve satisfactory pain relief.[61–63] Finnerup et al.[58] reviewed the pharmacotherapy for neuropathic pain in adults. Outcomes were generally modest even for effective drugs: in particular, NNTs were 3.6 (95% confidence interval [CI] 3.0-4.4) for TCAs and 6.4 (95% CI 5.2-8.4) for the SNRI anti-depressants duloxetine and venlafaxine. There was no evidence for a dose-response effect for amitriptyline. Combined NNH was 13.4 (9.3-24.4) for TCAs and 11.8 (9.5-15.2) for SNRIs. Low-dose amitriptyline (25 mg/day) for chronic low back pain did not improve outcomes at six months with no improvement in pain intensity, but there was a reduction in disability at three months.[64] When anti-depressants are used for chronic pain, the most prevalent adverse effects from anti-depressants were dry mouth, dizziness, nausea, headache, and constipation.[65] Risk for withdrawal because of adverse effects was highest for desipramine followed by venlafaxine and duloxetine. TCAs are associated with increased mortality in cases of intentional or accidental overdose, and their side effects profile and tolerability require careful dose titration and frequent monitoring, which substantially limits their wide use.[66] Minor side effects are common and more common with duloxetine 60 mg and particularly with 120 mg daily than 20 mg daily, but serious side effects are rare.

Chemotherapy-induced peripheral neuropathy (CIPN) is common among cancer patients who undergo chemotherapy with platinum analogs, taxanes, vinca alkaloids, epothilone, bortezomib, and thalidomide. Chemotherapeutic agents can damage nervous system structures and, depending on the individual compound, can cause various neuropathies that affect different structures, including large and small fibers and autonomic function.[67] The effects of chemotherapy on the nervous system vary among the different classes of drugs, depending on the specific physical and chemical properties of the drug used and its single or cumulative doses. The mechanism by which chemotherapeutics damages nervous system structures and causes CIPN is multifactorial and involves microtubule disruption, oxidative stress and mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage, immunologic processes, and neuroinflammation.[68] The mechanisms of injury are complex and interested readers are referred to the review by Carozzi et al.[69] When patients experience drug-induced chronic neurotoxicity that necessitates intervention beyond dose reduction or discontinuation, the strongest evidence supports the use of duloxetine.[70] However, other anti-depressants have not shown a similar benefit. Furthermore, the best available data support a moderate recommendation for

TABLE 33.6 Classification of Anti-depressants

Drug Type	Example	Comment
Norepinephrine-dopamine reuptake inhibitors (NDRI)	Bupropion	Acts selectively to inhibit the noradrenergic and dopaminergic reuptake transporter pump systems. Side effects include anxiety, insomnia or sedation, weight loss, and may be excessively activating for some patients. Seizures may occur at dosages above 450 mg/day.
Serotonin noradrenaline reuptake inhibitors (SNRIs)		Mixed action on both NE and serotonin. Used in the treatment of pain disorders, including neuropathies and fibromyalgia. SNRIs are also used in the treatment of generalized anxiety disorder, stress urinary incontinence, and vasomotor symptoms of menopause. Pharmacologic properties are dose dependent. At low doses, behave essentially like an SSRI; while at medium doses, additional NE reuptake inhibition occurs, and at high-to-very high doses, weakly inhibit the reuptake of dopamine.
	Duloxetine	Side effects include nausea, dry mouth, constipation, dizziness, and insomnia.
	Venlafaxine	Serotonin reuptake inhibition in dosages below 150 mg/day; mixed serotonin and noradrenergic reuptake inhibition in dosages above 150 mg/day Side effects may include headache, nausea, sweating, sedation, hypertension, and seizures.
	Desvenlafaxine	Major active metabolite of venlafaxine. X10 times more potent inhibiting serotonin than norepinephrine uptake.
Selective serotonin reuptake inhibitors (SSRIs)		Proven efficacy in panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, and bulimia, with encouraging findings in social phobia, post-traumatic stress disorder. Side effects of SSRIs may include nausea, sedation, decreased libido, sexual dysfunction, headache, and weight gain.
	Citalopram	QT prolongation.
	Escitalopram	(S)-enantiomer of citalopram.
	Fluoxetine	Can cause activation (take during daytime). Because of a long half-life and active metabolites, rare symptoms of discontinuation or withdrawal symptoms if abruptly stopped.
	Paroxetine	Can be sedating and thus taken at bedtime. Its anticholinergic side effects can affect cognition, especially in the elderly. Discontinuation/ withdrawal symptoms could develop if abruptly discontinued.
	Sertraline	
Serotonin receptors antagonist with serotonin reuptake inhibition (SARI)	Trazodone	Moderate-to-strong serotonin receptor(s) antagonism with a weak serotonin reuptake transporter inhibition. Side effects include sedation and drowsiness, tachycardia, and priapism (rarely).
Tricyclic anti-depressants (TCAs)		"Gold standard" anti-depressants. Among the best studied and most commonly used are the first-generation TCAs, which are mixed reuptake inhibitors with both NE and serotonergic 5-HT effects such as amitriptyline, imipramine, and doxepin.
	Amitriptyline	Most potent anticholinergic; cautious use in elderly.
	Clomipramine	
	Desipramine	As secondary amine, fewer anticholinergic effects.
	Doxepin	Most potent antihistamine effects.
	Imipramine	
	Nortriptyline	Acts by inhibiting the reuptake of NE and serotonin 5-HT and possesses central anticholinergic activities. As secondary amine, fewer anticholinergic effects.
	Desipramine	
Noradrenergic α2-receptor antagonist with specific serotonergic receptors-2 and -3 antagonism (NASSA)	Mirtazapine	Enhances release of NE and 5-HT1A-mediated serotonergic transmission. Side effects include drowsiness, dizziness, anxiety, confusion, increased appetite, and weight gain.

treatment with duloxetine.[71] CIPN trials were also inconclusive regarding tricyclic anti-depressants (such as nortriptyline) and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine.[71] Anti-convulsants, such as gabapentinoids, have not been proven effective for patients with CIPN.[70] Duloxetine, when used for diabetic peripheral neuropathy and fibromyalgia, has efficacy for pain associated with diabetic neuropathy at doses >60 mg/day (not at lower doses).[72] The effect in fibromyalgia was likely achieved through a greater improvement in mental symptoms than in somatic physical pain.

Opioids

Opioids are extensively discussed in Chapter 48. Although some suggest that opioids are relatively ineffective for the management of neuropathic in chronic pain,[58,73] this has not been our experience and of others in cancer pain.[74–76] Clinical pathways have emerged as one of the key approaches to minimize unwarranted variation in care and improve both the quality and efficiency of care. When appropriately designed and implemented, oncology pathways are detailed with evidence-based treatment protocols for delivering quality cancer care for particular patient presentations that include the type and stage of disease.[77] Extrapolation from opioid prescribing recommendations, including the guideline for prescribing opioids for chronic pain from the Centers for Disease Control and Prevention,[78] and applying these to the cancer population is problematic as most of the recommendations have not included opioid outcomes in this particular population. Consequently, some professional oncology organizations and societies have issued policy and position statements on opioid therapy emphasizing continued access for cancer-related pain.[79–81] Continued use of opioids in oncology requires risk evaluation and strategies for continued monitoring in all patients, including those considered at high risk for opioid misuse or abuse or illicit substance use (Table 33.7).

Opioids have been classified as weak and strong opioids, based upon their affinity for the μ-receptor.[82,15] Distinct opioids may elicit very different intracellular responses and may ultimately have very different outcomes on behavior, including analgesic ability, addiction liability, and the risk for acute negative side effects such as respiratory depression.[83] The wide-ranging drug-specific differences among opioids in their pharmacokinetics and pharmacodynamics include opioid receptor biases and ligand biases at the opioid receptors, as well as differential interactions with the non-opioid system. These result in differential coupling and activation of intracellular signaling and likely accounts for diverse interactions with various biologic systems, such as the immune

TABLE 33.7 Risk Evaluation and Monitoring for Continued Opioid (All Doses) Therapy in Oncology Patients

All Patients	
Risk stratification	Screening tool such as ORT Personal history of substance abuse including prescription opioids, psychoactive medications, illicit substances, alcohol Family history of substance abuse including prescription opioids, psychoactive medications, illicit substances, alcohol Presence of adequate support system (family, friends, social)
Education on opioid use and safety	Risk versus benefit Informed consent for opioid therapy Safe medication keeping Adherence to prescription instructions Naloxone use
Regular ongoing screening and monitoring	Regular follow-up with pill counts/opioid reconciliation (telephone/telemedicine/clinic) or office visit Prescription monitoring program review at each refill Current opioid misuse measure at each clinic/office visit Review for the presence of aberrant drug behaviors Urine toxicology screening (to include alcohol, illicit drug, comprehensive panel for opioids) at minimum yearly or sooner as clinically indicated
Regular concomitant psychoactive medication review	Elimination of other psychoactive medications when possible Avoidance of concurrent long term use of benzodiazepines or Z drugs
High Risk Patients	
No evidence of current substance use	Regular review of medical indication for continued opioid use Referral for addiction specialist assessment (as indicated) Frequent (at least four times per year) random urine drug screening (to include alcohol, illicit drug, comprehensive panel for opioids) Consequences for unsanctioned substance/non-prescribed medication use, including alcohol
Evidence of current substance use	No initiation of controlled substance prescriptions with ongoing illicit substance use, including alcohol Referral for addiction assessment and management Frequent (at least four times per year or more frequently as clinically indicated) urine drug screening (to include alcohol, illicit drug, comprehensive panel for opioids) Elimination of other psychoactive medications when possible Consequences for unsanctioned substance/non-prescribed medication use, including alcohol

The use of an opioid contract is not considered mandatory in oncology care. High risk patients include patients with an opioid risk tool (ORT) score of ≥ eight; history of chemical coping or issues with prescription adherence; active problematic alcohol use, illicit drug or prescription drug abuse. Aberrant drug-related behavior is a behavior suggestive of a substance abuse and/or substance use disorder.

system and the dopaminergic reward system.[84] Three distinct opioid receptors have been cloned, mu (MOR), kappa (KOR), and delta (DOR), with different selectivity for individual endogenous peptides and the various opioids. The three opioid signaling systems have unique and counterbalancing roles as they relate to their regulation of pain, stress, and affect. Though the MOR is the main target for opioid analgesics, the DOR and KOR also regulate pain, and analgesia and the relative affinities of opioid analgesics for these receptors confer their unique properties. MOR agonists produce euphoria and promote stress coping. KOR agonists produce dysphoria and are associated with stress and negative affect. DOR is on the opposite end of the continuum describing mood, and DOR agonists have anxiolytic and anti-depressant activity.[85] Opioids mimic endogenous opioids and act by binding to the opioid receptors, thereby activating them with individual differences in receptor binding and signal transduction.[86] Additionally, G protein signaling can be selectively targeted.[87]

Opioids are the mainstay of pharmacotherapy for patients with moderate or more intense pain resulting from virtually any cancer-related etiology. The specific pathogenic mechanism that underlies a patient's cancer pain should not be a factor in deciding which opioid to use, as the mechanism of pain does not reliably predict the response to opioid therapy. This particularly applies to situations in which tumor-associated neuropathic mechanisms dominate the pain complaint. Opioids should be used as first line therapy in such situations, particularly if the pain is considered moderate to severe in intensity. In oncology, opioids have demonstrable benefits for neuropathic pain.[88–90] Factors influencing the selection of a particular opioid are listed in Table 33.8.

All clinicians who prescribe opioids for the treatment of cancer pain should be familiar with at least three different agents appropriate for the management of moderate to severe pain.[91] The regimen for opioid medications should generally provide around the clock analgesia with provision for rescue doses for the management of exacerbations of the pain not covered by the regular dosage. Predicting the effectiveness of extended release opioids requires knowledge of associated pharmacokinetics. The onset time and time to maximal concentration (Tmax) are particularly helpful. For the extended release opioids, the elimination half-life is not particularly useful because of altered absorption characteristics into the central compartment.

Opioids are effective after peripheral (topical, intra-articular), neuraxial (intrathecal, epidural, intracerebroventricular), or systemic (intravenous, oral, subcutaneous, sublingual, intranasal, transdermal) administration, although the final effects are highly dependent on the particular pharmacokinetic and pharmacodynamic features of each drug.[84]

TABLE 33.8 Factors Influencing the Selection of Opioid Therapy

Previous opioid exposure and preference
Severity, nature, and stage of disease
Age of patient
Extent of cancer, particularly hepatic and renal involvement altering normal opioid pharmacokinetics
Concurrent disease
Available formulations
Risk assessment for problematic opioid use

TABLE 33.9 Opioid-Related Side Effects

	Transient Side Effects
Nausea/ vomiting	Direct effect on CTZ Sensitivity of vestibular apparatus (activation of MROs in vestibular epithelium) Delayed gastric emptying (central and peripheral)
Pruritus	? agonism at MOR
Sedation	Disordered level of consciousness in which both arousal mechanisms and content processing are functional but attenuated Symptoms include feeling drowsy, sleepy, groggy, dizzy, dreamy, cloudy, mentally foggy, or lethargic Signs may include cognitive impairment, lack of coordination, slowed reaction time, and performance deficits
Respiratory depression	Consider synergistic effects from concomitant other centrally acting drugs Rule out other contributors (e.g. pneumonia, sleep apnea)
Urinary retention	Spinal cord opioid receptor activation ® bladder wall relaxation Increased parasympathetic activity to detrusor muscle
Persistent Side Effects	
Opioid-induced constipation	Enteral activation of opioid receptors resulting in gastric emptying, sphincter tone, and peristalsis Consider peripherally acting MOR antagonist (PAMORA) agents
Endocrine effects	? direct effect on opioid receptors within hypothalamus, pituitary, and testes Hypothalamic effect, gonadotropin-releasing hormone

CTZ = Chemoreceptor trigger zone.
MOR = Mu opioid receptor.

All clinicians involved in the treatment of cancer patients should be familiar with the most common types and dosages of opioids, as well as the management of the most common side effects (Table 33.9).[18]

Selected Opioids

Tramadol

Tramadol is a synthetic analog of morphine and codeine and was approved by the FDA to treat moderate to severe pain in adults. Formulations include immediate-release tablets, sustained-release tablets, and extended release capsules. It has a unique mechanism of action and pharmacologic effects that differ from those of other opioid drugs. It has opioidergic, noradrenergic, and serotonergic actions and also has modulatory effects on several mediators involved in pain signaling. Tramadol's active metabolite (M1) contributes significantly to its analgesic effect. Cmax is achieved approximately 2 h after oral administration, t1/2 is 5–6 h, and bioavailability of 68%–84%. The kidneys are responsible for 90%

excretion of tramadol and its metabolites; the remaining 10% is excreted through feces. Because of its hepatic metabolism and renal clearance, impairment in these systems may require dose modifications.

Serotonin syndrome may occur with concomitant administration of serotonergic psychotropic agents within recommended dosing parameters for fluoxetine, paroxetine, sertraline, venlafaxine, mirtazapine, citalopram, bupropion, and olanzapine. Certain serotonergic anti-depressants (i.e. paroxetine, fluoxetine) inhibit cytochrome P-450 2D6, elevating plasma concentrations of tramadol and further increasing the risk for serotonin syndrome. Importantly, tramadol is specifically contraindicated with monoamine oxidase inhibitors or within 14 days of discontinuing a monoamine oxidase inhibitor.[92] Tramadol side effects are varied. However, the most common events are nausea, followed by vertigo, dizziness, vomiting, tiredness, constipation, sweating, dry mouth, and sedation. The causes of seizures after tramadol exposure are unclear. There is limited, very low quality evidence from randomized controlled trials that tramadol produced pain relief in some adults with pain because of cancer.[93]

Tapentadol

Tapentadol, a centrally acting analgesic, has been proposed as the first agent in a new class of drugs (MOR-NRI) combining the two mechanisms of action μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI) in one molecule.[94] Because of its limited protein binding capacity, the absence of active metabolites, and significant microsomal enzyme induction or inhibition, tapentadol has a limited potential for drug-drug interactions.[95] Bioavailability is approximately 32% with t½ of 4 h for immediate-release formulations and 5–6 h for extended release. It shows moderate MOR agonist activity, pronounced NA reuptake inhibition, and minimal 5-HT effect. Clinical trials for chronic severe pain suggested that tapentadol provided equivalent or superior levels of pain relief for acute and chronic pain similar to oxycodone, hydromorphone, fentanyl, oxymorphone, and morphine and significantly less frequent gastrointestinal adverse events (nausea, vomiting, constipation) compared with fentanyl, morphine, hydromorphone, and oxymorphone.[96] From the limited data available for oncology pain, pain relief, and adverse events were comparable to morphine and oxycodone, with the most common adverse events being gastrointestinal (nausea, vomiting, constipation).[96]

Hydrocodone

Hydrocodone is a full opioid agonist with relative selectivity for the μ-opioid receptor, although it can interact with other opioid receptors (δ and κ) at higher doses.[97] Human PK studies indicate that the conversion of hydrocodone to its primary metabolite, norhydrocodone, and lesser metabolite, hydromorphone, is mediated by the cytochrome P450 enzyme system. Some authors suggest that hydrocodone is a pro-drug and requires metabolism to hydromorphone for therapeutic benefit and that pain relief correlates with plasma hydromorphone concentrations rather than hydrocodone.[98] Immediate-release hydrocodone is available as a combination product (acetaminophen, ibuprofen), and single entity hydrocodone only available as extended-release formulations. Hydrocodone is also an antitussive and indicated for cough in adults. The analgesic efficacy can be highly variable and devoid of therapeutic effect in some patients, likely because of CYP2D6 polymorphisms.[99] Data regarding the use of hydrocodone in oncology is limited. When low-dose hydrocodone (25 mg/day) was compared to tramadol (200 mg/day) in patients with chronic cancer pain, hydrocodone was not superior in terms of analgesic efficacy, and tramadol produced more mild side effects than hydrocodone.[100]

Methadone

Methadone is available as a racemic mixture of two stereoisomers – L-methadone (pharmacologically active isomer) and D-methadone. L-methadone is eight to 50 times more potent than D-methadone in humans and is believed to be almost entirely responsible for its analgesic properties. Because of its large volume of distribution and its long half-life, methadone tends to accumulate in adipose tissues, especially after repeated doses. It is 60%–90% bound to plasma proteins, and its bioavailability after oral administration is 70%–90%. Tmax averages 2.5–4.4 h following oral administration. On average, the half-life of methadone is around 24 h, but it may vary as much as from 8 to 120 h depending on an individual patient's adipose tissue composition. Because of its long, biphasic elimination half-life, it may take up to ten days to reach steady-state serum levels. Dosage adjustment is not required in renal or hepatic insufficiency or hemodialysis. Methadone is primarily metabolized by N-demethylation to an inactive metabolite. Cytochrome P450 enzymes are responsible for the conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine. One of the enzymes, CYP3A4, is also involved in the metabolism of other drugs: benzodiazepines, calcium antagonists, macrolide antibiotics, and anti-convulsants (carbamazepine). Its activity is strongly inhibited by ketoconazole, fluoxetine, and grapefruit juice (large amounts). Because CYP3A4 is inducible, it can result in drug interactions with other drugs that are also dependent on that enzyme for metabolism. This may directly affect plasma concentrations of methadone with CYP3A4 inducers decreasing plasma levels and inhibitors increasing blood levels (Table 33.10).

Managing the Cardiac Effects of Methadone

The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. While the ability of methadone to block the NMDA receptor has been demonstrated in animal models,[101] it is unclear if this has clinical relevance at normal doses. Studies for this indication are limited with very low quality evidence of efficacy and safety.[102] In cancer pain, the analgesic benefits of methadone appear similar to morphine.[103] Our experience is that this is an excellent opioid for pain management but should be avoided in situations of rapidly changing pain complaints where frequent changes in opioid dosing are anticipated (e.g. uncontrolled tumor pain). Further, many drugs used in oncology (e.g. tyrosine kinase inhibitors, 5-HT inhibitor antiemetics, monoclonal antibodies) can also prolong QTc.

Buprenorphine

Buprenorphine is a semi-synthetic high affinity partial agonist at μ-opioid receptors and an antagonist at κ receptors with a ceiling effect on sedation and respiratory depression without a clinically relevant ceiling on pain relief.[104] The high receptor affinity results in a slow dissociation from the receptor and prolonged activity. Precipitated withdrawal can result if buprenorphine is introduced in the presence of other opiates with lesser binding affinities. Unlike other opioids, buprenorphine exhibits a ceiling effect for respiratory depression (acts as a partial agonist) but not for pain relief.[105] Data in opioid-naive volunteers indicate that buprenorphine

TABLE 33.10 Drug Effects on Methadone Levels and QTc Interval

Drug	Effect on Methadone Levels	Effect on QTc Interval
Antibiotic/antifungal		
Ciprofloxacin	□	
Clarithromycin	□	□
Erythromycin	□	□
Ketoconazole	□	
Fluconazole	□	
Rifampin	□	
Anti-convulsants		
Carbamazepine	□	
Phenytoin	□	
Antipsychotics		
Quetiapine	□	□
Benzodiazepines/Z–Drugs		
Alprazolam	□	
Diazepam	□	
Lorazepam	□	
Midazolam	□	
Triazolam	□	
Zopiclone	□	
Serotonin Noradrenaline Reuptake Inhibitors		
Fluoxetine	□	
Fluvoxamine	□	
Nefazodone	□	
Paroxetine	□	
Sertraline	□	
Tricyclic Anti-depressants		
Amitriptyline		□
Desipramine		□
Imipramine		□
Nortriptyline		□

causes dose-dependent respiratory depression that levels off at greater buprenorphine doses.[106] Also, in contrast to other opioids, buprenorphine has a pronounced antihyperalgesic effect, which may be because of its κ-receptor antagonism.[105] It is extensively metabolized through 14-N-dealkylation by the hepatic CYP3A4 (primary pathway) to norbuprenorphine with 50%–70% eliminated fecally. Routes of administration are typically oral, sublingual, buccal, and transdermal. It is often formulated with naloxone to deter diversion. Administration of buprenorphine via the sublingual route can quickly reach effective plasma concentrations (onset of effect is 30–60 min with Tmax at about 90–100 min). Oral formulations of buprenorphine have low bioavailability with only 10% of the intravenous route if swallowed and only between 30% and 50% bioavailability with the sublingual administration. The bioavailability of buccal buprenorphine is 46%–65%. In low doses, buprenorphine can only partially activate the μ-opioid receptor. In moderate doses, the buprenorphine's opioid agonist effect reaches a plateau (ceiling) such that any further dose increase is unlikely to enhance analgesia. In high doses, buprenorphine functions as an opioid antagonist to further limit its analgesic effect.[107] The role of buprenorphine in the management of chronic pain is questionable, with few high quality, unbiased studies performed in this area.[108] Two buprenorphine formulations are approved by the FDA for the management of pain—buprenorphine buccal film (Belbuca^{R}) and buprenorphine transdermal (Butrans^{R}). The transdermal is intended for use for patients requiring a MED <80 mg/day and the buccal for patients up to 160 mg/day.

The amount and quality of data on the use of buprenorphine for cancer pain are low.[109,110] Potential advantages in oncology pain management include alternate routes of administration, a presumed reduced risk of opioid-induced respiratory depression, and lack of QTc prolongation (compared to methadone). However, the use of buprenorphine potentially complicates acute pain management issues in oncology (post-surgical patients, severe mucositis) as the use of concomitant full μ-opioid agonists may be problematic. The perioperative management of patients using buprenorphine has not been definitively answered and for which there is no widespread consensus.[111] While a theoretical ceiling effect may exist for buprenorphine and respiratory depression, it can still cause significant adverse effects on respiratory function. One review suggests that there was no difference in respiratory depression or sedation in an acute pain setting compared with morphine.[112] Deaths have also resulted from buprenorphine intravenous misuse or concomitant sedative drug ingestion, such as benzodiazepines. In these situations of abuse, misuse, or association with elevated doses of psychotropic drugs, buprenorphine may cause severe respiratory depression.[113] Furthermore, the unique pharmacodynamics of buprenorphine as a semisynthetic opioid with a significant affinity for μ receptors leads to further complexities associated with naloxone reversal.

Use of Psychoactive Drugs in Oncology

The WHO has defined psychoactive substances as substances that affect mental processes such as cognition and comprise both legal and illegal substances.[114] A psychoactive medication may result in stimulation or depression of the central nervous system, potentially resulting in changes to motor function, thinking, behavior, perception, awareness, or mood. Table 33.11 lists examples of different categories of psychoactive medications commonly used in oncology.

Negative outcomes associated with polypharmacy may occur in patients taking as few as four drugs at any time[115] and are associated with older patients with comorbidities, including cancer.[116,117] Polypharmacy increases the risk of drug-drug interactions, drug-disease interactions, and adverse drug reactions. The risk of drug-drug interactions is high in oncology because of the large number of concomitant medication use,[118,115] and is associated with older patients with comorbid illnesses, including cancer.[116,117] Patients treated systemically for cancer are particularly at risk for drug-drug interactions. Typically, patients with cancer receive a high number of drugs concomitantly, including cytotoxic agents, hormonal

TABLE 33.11 Categories of Psychoactive Medication Use

Medication Class	Example
Non-opioid Analgesics	Tizanidine
Anti-depressants	Amitriptyline, nortriptyline, trazodone
Anti-convulsants	Gabapentinoids,
Anxiolytic/Sedative/ Hypnotics	Benzodiazepines
Sleep Aids	Z drugs (zolpidem, zaleplon, eszopiclone)
Muscle Relaxers	Carisoprodol, methocarbamol, tizanidine, cyclobenzaprine
Stimulants	Dextroamphetamine, lisdexamfetamine, methylphenidate, dextroamphetamine,
Neuroleptics	Olanzapine, haloperidol

agents, targeted agents, and supportive care agents, among medications prescribed to treat comorbidities. Drug-drug interactions from the combination of opioids with other drugs may result in sedation/respiratory depression, other CNS symptoms, impairment of pain control and/or opioid withdrawal, and other issues.[119] Morphine may also indirectly be affected by renal failure caused by other agents or diseases. Additionally, other drugs with sedative effects can cause pharmacodynamic interactions with an opioid. A typical observation is the combination of an opioid and a benzodiazepine, both contributing to sedation. Concurrent use of benzodiazepines in opioid users has also been associated with death from drug overdose,[120] and concurrent use of prescription opioids and sedative-hypnotics, even at low to moderate opioid doses, increases opioid mortality risk.[121] CNS symptoms (other than sedation and respiratory depression) associated with opioids include hyperactive or hypoactive delirium with or without hallucinations, serotonin toxicity, myoclonus, hyperalgesia, extrapyramidal symptoms, catatonia, and neuroleptic malignant syndrome. Because of the increased risk of osteoporosis and the extensive use of CNS-depressant drugs, cancer patients are particularly at risk for fractures.[122] Prescribed CNS-depressant drugs can result in an up to 47% increased risk of falls.[123] The prescription of combinations of CNS-depressant drugs may even further increase this risk.[124] Because of the increased risk of osteoporosis and the extensive use of CNS-depressant drugs, cancer patients are particularly at risk for fractures.[122] Prescribed CNS-depressant drugs can result in an up to 47% increased risk of falls.[123] The prescription of combinations of CNS-depressant drugs may even further increase this risk.[124]

Adjustment disorder, major depressive disorder, and anxiety disorder are the most common psychiatric comorbidities in cancer patients, with the persistence of these issues into survivorship.[125] Mild neurocognitive disorders can be secondary to chemotherapy or chemotherapy-associated with radiation therapy, which can cause impairment of memory, attention, concentration, learning functions, calculation, and visual-spatial perception.[126] A 2012 study from the Netherlands indicated that all classes of psychotropic drugs were more frequently prescribed to cancer patients than controls.[127] Furthermore, psychoactive medications may be used for many nonpsychiatric complaints in cancer patients, such as in the treatment of fatigue, insomnia, and pain. Psychoactive medications can affect neurocognitive functioning. Both TCAs[128,129] and SSRIs[130] impair sustained attention and memory in non-depressed adults. Anti-convulsants have negative effects on cognition in patients with epilepsy and may also produce untoward cognitive effects on attention, memory, and psychomotor speed in healthy adults.[131] These effects may emerge in a dose dependent fashion,[132] suggestive of a direct effect of these medications on specific neurocognitive processes. Anti-depressants, anti-convulsants, CNS stimulants, and neuroleptic medications were associated with reports of impaired functioning across multiple domains of neurocognition in adult survivors of childhood cancer.[133] Among all medications, central nervous system stimulants showed the largest associations with impaired task efficiency, organization, and memory.[133] Sedation, mental confusion, and delirium are common with all antipsychotic medications. Benzodiazepines and Z drugs (drugs taken for insomnia - zolpidem and zopiclone) are commonly used in patients with cancer for the management of symptoms such as sleep disturbance, anxiety, agitation, and dyspnea. Side effects of benzodiazepines include confusion, drowsiness, amnesia, and ataxia. The impact of the use of anti-depressants on depression in patients with cancer is unclear, and use in oncology should be considered on an individual basis and the choice of agent prescribed based on the data on anti-depressant efficacy in the general population of individuals with major depression considering that data on medically ill patients suggest a positive safety profile for the SSRIs.[134,133]

For some oncology groups, there is a general trend for medication use to markedly increase from precancer baseline to active care, followed by a decrease in first year survivorship, although not returning to baseline levels.[135] Polypharmacy is also prevalent in advanced cancer, with a reported mean and median number of prescribed drugs ranging from three to nine.[136] Older patients with cancer (aged 65 years and older) more often had polypharmacy than younger patients. In a study of 5,950 veterans with metastatic cancer, patients with extensive opioid use, 64% also received anti-depressants, and 38% received three or more classes of psychotropic medications.[137] Polypharmacy could be even more important in older oncology patients receiving chemotherapy, who tend to be more vulnerable to the adverse effects of medications than older adults without cancer.[138] The American Geriatrics Society Beers criteria are a tool for evaluating the appropriateness of medication use for older adults and endorsed by the American Geriatrics Society.[139] These comprise a list of potentially inappropriate medications that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions. They are intended for use in adults 65 years and older in all ambulatory, acute, and institutionalized settings of care, except for the hospice and palliative care settings. The criteria are composed of five primary tables of guidelines: medications that are potentially inappropriate in most older adults; medications that are potentially inappropriate in patients with certain conditions; medications that should be used with caution; potentially clinically important drug-drug interactions that should be avoided; and medications that should be avoided or have their dosages reduced with varying levels of kidney function. Drugs mentioned in these criteria relevant to oncology pain management include TCAs (avoid use), antipsychotics (avoid except for short-term use as antiemetic during chemotherapy), barbiturates (avoid), benzodiazepines (avoid), Z drugs (avoid), Gi – metoclopramide (avoid, unless for gastroparesis with a duration of use not to exceed 12 weeks except in rare cases), NSAIDs (avoid chronic use, unless other alternatives are not effective and

the patient can take gastroprotective agent), and skeletal muscle relaxants (avoid). To avoid drug-drug interactions, avoid the use of opioids concurrently with benzodiazepines and avoid the use of opioids concurrently with gabapentinoids (except when transitioning from the former to the latter). The concurrent use of any combination of three or more CNS agents (anti-depressants, antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, antiepileptics, and opioids) have an increased risk of falls (all), and fracture (benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics) should be avoided with an attempt to minimize the number of CNS-active drugs. SNRIs should be avoided in patients with a history of falls or fractures. Of note, substantial harms can occur when opioids are used concurrently with benzodiazepines or gabapentinoids.

Oncology patients are frequently exposed to benzodiazepines to help manage common sequelae of cancer and its treatment, including anxiety and chemotherapy-related nausea. Long term cancer survivors (>10 years) in Norway with persistent or high-dose opioid use may also be prescribed benzodiazepines or benzodiazepine-like hypnotics.[140] The use of benzodiazepines may be particularly problematic with concurrent opioid use. Co-prescribing was associated may be associated with a significantly higher risk of death,[120] emergency room (ER) visits, or inpatient admission[141] than with the use of opioids alone. The FDA released a black box caution warning patients and providers about the potential risks of combined use.

The Opioid Epidemic and Cancer Pain

The opioid epidemic is discussed in Chapters 50 and 51. The widespread abuse of prescription opioids and a dramatic increase in the availability of illicit opioids have contributed to this problem.[142] Over and inappropriate medical prescribing, diversion and misuse of prescription opioids, a resurgence in heroin use, an increase in the abuse of illicit, and the availability of illicitly manufactured high-potency synthetic opioids such as fentanyl are likely major contributors to this problem. Overdose deaths related to opioids have dramatically increased. Identifiable characteristics associated with an elevated risk of opioid overdose include a history of overdose, a history of addiction to any substance (but particularly alcohol, benzodiazepines, or opioids), and health problems associated with respiratory depression or concurrent prescription of any medication that has a depressive effect on the respiratory system, such as benzodiazepines and sedative-hypnotics.[143] Abuse of opioids is a complex issue that is not solely related to the opioid used. Mental health disorders, genetic, environmental, and lifestyle factors are important contributors. Opioid abuse and misuse also occur for various reasons, including self-medication, use for reward, compulsive use because of addiction, and diversion for profit.[144] In a meta-analysis of 568,640 patients who had not used opioids in the six months prior and with a new diagnosis of any type of chronic non-cancer pain, the odds ratio for developing an opioid use disorder (OUD) was 14.9 for patients on chronic (> three months of use) low-dose (1–36 mg MED) opioids and 122.45 for patients on chronic high-dose (120 mg + MED) opioids, respectively, with the duration of opioid therapy more important than the daily dose in developing OUD.[145] Policy changes, including recommendations contained in Pain Management Best Practices Inter-Agency report,[146] and CDC guidelines[78] inform prescribers on best practices for using opioids in chronic pain. For chronic non-cancer pain, most recommendations caution against the use of opioids for chronic pain complaints.

Public and healthcare information has emphasized that addiction in the context of cancer pain and the use of opioids is rare or non-existent. The prevalence of opioid abuse in patients with cancer on opioid therapy is unknown, and most of the published data relate to non-cancer pain issues. Data about substance abuse in cancer patients and those seen in palliative care clinics have been scarce. Barclay et al.[147] found that more than 40% of cancer patients seen were moderate to high risk for opioid abuse as measured by the opioid risk tool; 62% of these at risk patients with a urine drug screen ordered had at least one abnormal result. However, most hospice and palliative care programs do not have substance abuse and diversion policies or report screening all patients.[148] In the complex milieu of complications of cancer and metastasis, including heterogeneous cancer biology, multiple drugs being used, pain, opioid analgesic use, and psychosocial factors, delineating the specific contribution of individual factors on survival is challenging. It is important to recognize that cancer patients are not immune to developing aberrant opioid and drug use behaviors. Patients who have ongoing anxiety, financial distress, and a prior history of alcoholism/illicit drug abuse are at increased risk.[149] Solutions for the opioid epidemic are complex and appear to have largely been focused on physician prescribing habits and regulating patient access to opioids.[150] Although well-intentioned, these regulations could inadvertently create an atmosphere that inhibits access to opioid pain treatment for cancer patients and cancer survivors. Withholding opioids from patients with advanced cancer pain has significant ethical implications. Clinicians should be concerned about problematic opioid use even in patients with advanced disease. Without screening or testing for opioid misuse or abuse, it is impossible to address and manage these issues. Standard precautions should include a risk assessment of opioid abuse in all patients, considering whether there is a risk of diversion or abuse, monitoring of adherence, the management of any known psychological or psychiatric conditions, and the monitoring of drug-related behaviors.[151] If problems are identified, these should be managed appropriately according to standard clinical guidelines with accommodation for continued oncologic care. The dynamic and frequently changing nature of oncology pain makes this particularly challenging.[149]

Prevention of Opioid Overdose

The opioid overdose epidemic in the United States has been closely associated with a parallel increase in opioid prescribing and with widespread misuse of these medications.[152] Long-term opioid therapy carries clinically significant risks, including motor vehicle collisions, sleep-disordered breathing, and accidental overdose.[153] All patients treated with opioids are at risk for overdose. Factors increasing that risk include end-organ (liver, kidney) dysfunction resulting in impaired clearance, pulmonary disease, sleep-disordered breathing, and concomitant use of psychoactive medications. Strategies to improve patient safety include patient screening and risk stratification, patient and community education and outreach concerning appropriate pain management, medication reviews/medication therapy management, education on safe storage and disposal, and distribution of naloxone/opioid rescue kits and training on their proper use. Prescription monitoring programs (PMPs) allow the assessment of a patient's prescription history (scheduled II and III medications). However, not all psychoactive medications are included in this monitoring program. Also, the program does not identify the prescription of

methadone for substance use disorder. PMPs can identify doctor shopping, concomitant benzodiazepine prescriptions, and evidence of undisclosed opioid prescriptions from other providers. Medication disposal boxes and community-based drug take-back events offer alternatives to storing unused opioids (or other controlled substances) at home. Hallmarks of OUD include emotional volatility and signs of problematic medication use, such as taking more medication than prescribed, using opioids for reasons other than pain, and frequent loss of medication or early refills. Several instruments are used clinically to screen for problematic opioid use (see Chapter 51).

Prescribers must carefully weigh potential benefits against the risks of opioid-related adverse events and overdose for all encounters involving prescription opioids, and if patients are to be continued on long-term opioids, informed consent should be obtained. Patients with or who are subsequently identified as having an OUD require specialized treatment with professional addiction care. With ongoing oncology care issues, a co-management model for pain and substance use disorder is likely ideal. Ideally, a carefully planned structure of care should be in place for patients receiving chronic opioid therapy. Opioids should be primarily prescribed for improvement of function (defined on an individual basis) and not for reductions in pain intensity scores. Opioid dose escalation among patients with chronic pain is not associated with improvements in Numeric Rating Scale pain scores.[154] Before medication refills, an assessment of pain, functional status, safety, and other pertinent information should be conducted. Patients should provide pill counts and are given specific use dates for each prescription. PMP should be routinely checked along with the utilization of mass spectrometry urine drug tests based on opioid morphine milligram equivalent per day. This comprehensive based structure is labor-intensive and understandably may not be easily replicable in every practice. However, we consider this approach as it is essential for the continued and safe prescribing of opioid doses in this patient population who may benefit from continued use.

Intravenous Infusions for Cancer Pain

Lidocaine, an amide local anesthetic, inhibits voltage-gated sodium channels resulting in a reversible block of action potential propagation, but its exact analgesic mechanism is unknown. Preclinical and clinical evidence, particularly for acute and chronic pain, indicates that IV lidocaine has antihyperalgesic effects and by infusion for chronic neuropathic pain may reduce spontaneous pain, allodynia, and hyperalgesia.[155] Most studies advocate an initial bolus of 1–2 mg/kg followed by continuous infusion of 2–4 mg/kg/h, resulting in plasma concentrations of 1–3 mcg/mL.[156] Lidocaine and oral analogs (mexiletine, tocainide) were considered safe and better than placebo in clinical trials for non-cancer neuropathic pain.[157] Evidence for cancer-related pain is more limited, and there is wide variation in recommendations for use. Sharma et al.[158] demonstrated in 50 opioid-refractory cancer patients that a 2 mg/kg bolus and 2 mg/kg infusion over 1 h resulted in pain relief lasting a mean of 9.34 ± 2.58 days after the single infusion. Side effects observed were tinnitus, perioral numbness, sedation, lightheadedness, and headache. These were self-limited and did not require any intervention except for one patient. However, the role of systemic lidocaine in the management of tumor-associated pain is not defined. For cancer-related pain, the frequency of administration needed for the benefit and sustainability of analgesic efficacy is unknown.

Ketamine, an NMDA receptor antagonist, at subanesthetic doses may alleviate various chronic and neuropathic pain complaints.[159] A Cochrane review in 2017 concluded that there was insufficient evidence for the use of ketamine (administered intrathecally, by intravenous bolus, and subcutaneously) as an opioid adjunct in cancer pain.[160] In this review, the study using intravenous bolus administration, ketamine caused hallucinations in four of ten participants. In the rapid dose escalation/high-dose (500 mg) subcutaneous ketamine study, there was almost twice the incidence of adverse events in the ketamine group. Adverse events are most commonly somnolence, feelings of insobriety, nausea/vomiting, hallucinations, depersonalization/derealization, and drowsiness.[161] In a randomized, double-blind study of subcutaneous ketamine (at three dose levels of 100 mg/24 h, 300 mg/24 h, 500 mg/24 h for a five day schedule) for cancer pain, Hardy et al.[162] reported that the number needed to treat was 20 and the number needed to harm was six, suggesting no clinical benefit from ketamine as an adjunct. To date, subcutaneous or intravenously administered ketamine has not been shown to be effective in cancer pain.[163]

Intrathecal Therapies for Cancer Pain

Intrathecal therapies are discussed in Chapter 72. Intrathecal therapy involves the administration of drugs directly into CSF and to CNS receptor sites. Therapy may be delivered by bolus injection or by infusion. Options for drug delivery include an externalized catheter system (percutaneous or tunneled), a fully implanted pump (subcutaneous electronic pump with a tunneled catheter into the intrathecal space), or into the intraventricular system via an intracerebroventricular (ICV) device such as Ommaya reservoir. Administration of drugs via an Ommaya reservoir is typically for anti-neoplastic therapy, and most of the experience of ICV infusion of morphine has been from the 1980s and 1990s.[164] This route is not commonly used for oncology pain management. Drugs most commonly infused for spinal administration include opioids and bupivacaine. Compared to epidural administration, intrathecal drug delivery has higher analgesic efficacy and lower rates of treatment failure.[165] Although implanted drug delivery systems have been advocated for the management of cancer pain,[166] we advise against such systems in the management of patients undergoing active oncologic care. The complexity of programming, organizational challenges related to dose changes and pump refills, and potential safety issues in immunocompromised patients with low platelet counts are problematic. The use of tunneled externalized infusions systems such as those advocated by Nitescu, Sjoberg, et al. has potential for the management of intractable pain that require the administration of intrathecal bupivacaine.[167–173] Such systems allow for easy adjustment and titration of intrathecal bupivacaine doses. However, the administration of bupivacaine in such systems is usually significantly functionally limiting and again is not usually indicated in patients with active oncologic treatment.

Vertebral Augmentation (Vertebroplasty, Kyphoplasty)

Metastatic tumors to the spine or primary diseases such as multiple myeloma can cause painful vertebral compression fractures. Pain associated with these processes may require surgical treatment or anti-neoplastic therapy such as radiation treatment. Patients with

intractable pain who are not responsive to conservative therapy, including analgesics, or who are not surgical or radiation therapy candidates, may benefit from vertebral augmentation techniques assuming no other contraindications to this technique. In an extensive review involving 3,391 citations, of which 111 clinical reports (4,235 patients) evaluated the effectiveness of vertebroplasty (78 reports, 2,545 patients) or kyphoplasty (33 reports, 1,690 patients) for patients with mixed primary spinal metastatic cancers, multiple myeloma, or hemangiomas, the authors concluded that vertebral augmentation could significantly reduce pain intensity, decrease opioid needs, and improve functional disabilities.[174] In oncology, the procedure is most often considered for fractures related to multiple myeloma or those induced by steroid therapy. A consensus statement from the International Myeloma Working group recommended that myeloma patients with significant pain at a fracture site and without neurologic compromise should be offered augmentation, and the procedure should be performed within four to eight weeks unless there are medical contraindications. As patients with myeloma are susceptible to multilevel fractures, the total number of fractures should be limited to three at a time.[175] Long term (>six months) steroid use may cause osteoporosis which is associated with an increased fracture (vertebral and non-vertebral) risk.[176] There is also an increased fracture risk in patients exposed to intermittent high-dose oral steroid therapy.[177] The role of vertebral augmentation in treating acute or subacute osteoporotic vertebral fractures in routine practice is controversial and has not been validated consistently.[178,179]

Neurolytic Autonomic Plexus Blocks

These blocks typically include neurolysis of the celiac plexus and superior hypogastric plexus. The role of neurolytic celiac plexus blocks versus systemic analgesic therapy alone in the management of intractable tumor-associated intra-abdominal visceral pain is well established, particularly for the management of pain associated with pancreatic cancer.[180,181] Different techniques have been described to denervate the celiac plexus. Extensive tumor involvement of the celiac axis may not result in adequate denervation of the plexus with approaches specifically targeting the celiac plexus because of tumor infiltration of the plexus.[182] In this situation, our preferred denervation technique is bilateral retrocrural neurolysis of the thoracic splanchnic nerves.[183–185] Plancarte[186] introduced the option of superior hypogastric plexus block for the management of chronic cancer-related pelvic visceral pain. Although the block is considered relatively safe for pelvic associated pain, there is a need for large prospective studies to determine efficacy in cancer pain management.[187,188] It is important to remember that both of these blocks modify only nociceptive visceral pain and will not affect other potential sources of pain that are somatic or neuropathic in origin. For example, patients with pelvic disease that extends to the pelvic side wall (somatic) or involve neural plexuses (sacral) will not benefit from a superior hypogastric plexus block.

Summary

The optimal method of managing cancer-related pain is to diagnose the factor(s) contributing to the pain complaint. This disease-based (in contrast to symptom management) model of pain management focuses on the source of pain, and in patients with tumor-associated pain, therapy (not exclusively pharmacologic) should be directed to modify the source of that pain. These options typically include surgical, chemotherapeutic, and radiation oncologic options. Management of pain in cancer survivors is also complex, and models for the management of chronic non-cancer pain do not apply. Inadequate treatment of cancer pain continues to be an issue over the last three decades.[9,189,190] The humanitarian impact of cancer pain management should not be forgotten. Cancer pain profoundly impacts a patient's quality of life with physical, psychological, and social consequences. It is incumbent on healthcare professionals involved in the care of cancer patients to educate themselves on the complexities of pain and methods of management that focus on improving function and overall quality of life. Commonly cited barriers to effective cancer pain management among healthcare providers were fear of drug addiction, tolerance of medication, and side effects of opioids continue to be an issue.[191] These issues are even more problematic in an era of concerns for opioid overprescribing. The overall approach for oncology pain management should focus on a disease-based model of pain that focuses on routine pain assessments, uses both pharmacologic and nonpharmacologic interventions, and requires ongoing reevaluation of the patient and the effectiveness of the treatment strategy. The emergence of new pain problems must be assessed, and the treatment plan modified appropriately. Oncology healthcare systems require a supportive pain management infrastructure to allow for longitudinal care of the course of a patient's treatment.

Key Points

- Undertreatment of cancer pain remains problematic, with the prevalence of pain remaining high in survivorship.
- The guiding principle for pain management should be focused on improvement in function with a reduction in pain intensity as an ideal.
- Adequate management of cancer pain depends on identifying the source and making an accurate diagnosis of the underlying cause(s) of pain and contributing factors.
- Pharmacologic therapy is the primary treatment for cancer pain, but radiotherapeutic, anesthetic, neurosurgical, psychological, physiotherapeutic, spiritual, and social interventions all play roles in adequate cancer pain management.
- Opioids are commonly used to treat moderate or severe cancer pain, but there is substantial interpatient variability in opioid responsiveness. Therefore clinicians should be familiar with different opioid options for the appropriate management of cancer-related pain.
- Multiple psychoactive medications can be hazardous. Frequent efforts should be made to eliminate all unnecessary or ineffective medications that detract from the primary goal of opioid use and improved function.
- Responsible opioid prescribing practices are paramount in managing oncology pain.

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34

Evaluation and Treatment of Neuropathic Pain Syndromes

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Introduction

Neuropathic pain comprises a wide range of heterogeneous conditions. Various types of neuropathic pain may have distinct pathophysiologic causes and different clinical signs and symptoms. Despite the diversity of conditions classified as "neuropathic pain," many potentially share common underlying mechanisms of nociception, including neuronal hyperexcitability, but others may not. This may, in part, explain why certain analgesic agents are relatively effective for a wide range of neuropathic pain states but why notable exceptions exist that appear to be resistant to conventional "neuropathic" pain therapy. A group has been assembled to address the inconclusive research on "neuropathic" pain and to operationalize and specify definitions and criteria for conditions to be referred to as neuropathic pain (Box 34.1).[1] This work should lead to a more reductionist approach to the study of neuropathic pain and effective therapies for specific disease processes.

This chapter focuses on some of the more common states of "neuropathic" pain as defined by the sensitive but non-specific definition of the International Association for the Study of Pain (IASP). These conditions include postherpetic neuralgia (PHN), painful diabetic peripheral neuropathy (DPN), human immunodeficiency virus (HIV) painful sensory neuropathy, and chemotherapy induced peripheral neuropathy (CIPN). While complex regional pain syndrome (CRPS) is considered nocicplastic in nature, it is also discussed in this chapter.

Complex Regional Pain Syndrome

The term *CRPS*, which denotes both types one and two, originated from a history of different names appointed by individuals who made particular observations. In 1864 Silas Weir Mitchell made an important observation of Civil War soldiers when he noticed that they suffered from burning pain and muscle atrophy at the sites of their injuries caused by gunshot wounds.[2] He called this "causalgia," which is derived from the Greek words *kausis* (burning) and *algos* (pain). In 1900 at a lecture in Germany, Paul Sudeck stated that this syndrome could not only extend from the initial insult but also had an inflammatory component.[2] The name Sudeck's dystrophy was applied in his honor. Half a century passed before the discovery that invasive procedures that block the sympathetic nervous system provide further relief of pain symptoms. Because of the success of these methods, Evans renamed the syndrome "reflex sympathetic dystrophy."[3] Over the years, cases arose in which patients lacked a trophic component, sympathetic involvement was absent, or there was no evidence of reflex involvement. These exceptions led to a meeting in 1993 by the IASP at which the term "*complex regional pain syndrome*" was formulated and subsequently published the following year.[4] The most commonly used clinical diagnostic criteria for CRPS types one and two are low in specificity but high in sensitivity, which has led to overdiagnosis of the pain syndrome.[5] This has made it difficult to obtain accurate epidemiologic data for CRPS or to perform rigorous studies of the pathologic state. In 2007, research criteria (also known as the Budapest criteria) were published that included objective signs of pathology characteristic of patients with CRPS (Box 34.2).[6] These criteria had good specificity and sensitivity. Although they were initially intended for research use, this was later revised to include both a clinical and research set of criteria commonly used for diagnosis.

• BOX 34.1 Updated Definition of Neuropathic Pain

IASP Definition:[323] 2017

"Pain caused by a lesion or disease of the somatosensory nervous system"

Revised Research and Clinical Definition:[1] 2007

"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"

IASP, International Association for the Study of Pain.

Pathophysiology

There are two types of CRPS, known as type one and type two (Box 34.3). They differ because type two has evident nerve injury, whereas type one assumes an injury to the nerve or nerves. A consistent finding in both types of CRPS is the discrepancy between the severity of the symptoms and the severity of the inciting injury. In addition, symptoms have the propensity to spread in the affected limb in a pattern not restricted to the specific nerve's area of innervation. CRPS is characterized by intense burning pain with resultant hyperalgesia or allodynia. It may be associated with local edema and autonomic involvement, such as changes in skin color and sweating and increased or decreased skin temperature in the affected area. There may also be trophic changes in the skin, hair, and nails in the affected site (see Box 34.3). Although many

• BOX 34.2 Difference Between the IASP Criteria and the Budapest Criteria for the Diagnosis of CRPS

IASP Criteria for the Diagnosis of CRPS*

1. Presence of an initiating noxious event or reason for immobilization
2. Disproportional pain, allodynia, or hyperalgesia from a known inciting event
3. Sign or symptom of any evidence showing edema, skin changes, blood flow, or abnormal sudomotor activity in the region of the pain
4. No other condition that would otherwise explain the degree of pain or dysfunction

Budapest Criteria for Diagnosis of CRPS

1. Presence of continued disproportional pain from the known inciting event
2. Must report at least one symptom in three of these four categories:
   - Sensory: hyperesthesia, allodynia
   - Vasomotor: temperature asymmetry, changes in skin color
   - Sudomotor/edema: edema, changes in sweating, sweating asymmetry
   - Motor/trophic: decreased range of motion, motor dysfunction (tremor, weakness, dystonia), trophic changes (hair, nail, skin)
3. Must report at least one sign in two or more of these categories at the time of evaluation:
   - Sensory: hyperalgesia to pinprick, allodynia to touch, or joint movement
   - Vasomotor: temperature asymmetry, color asymmetry
   - Sudomotor/edema: edema, asymmetric sweating, sweating changes
   - Motor/trophic: decreased range of motion, motor dysfunction, trophic changes
4. No other condition that would otherwise explain the degree of pain or dysfunction

Budapest Clinical Criteria[6,42]

At least one symptom in three or four symptom categories
At least one sign in two or more sign categories

Budapest Research Criteria

At least one symptom in all four symptom categories
At least one sign in two or more sign categories

*If seen without any major nerve damage, the diagnosis is CRPS type one; if seen with evidence of nerve damage, the diagnosis is CRPS type two.
CRPS, Complex regional pain syndrome; *IASP*, International Association for the Study of Pain.

• BOX 34.3 Difference Between CRPS Type One and Two

CRPS Type One (Reflex Sympathetic Dystrophy)*

1. The presence of an initiating noxious event or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. This diagnosis is excluded by conditions that would otherwise account for the degree of pain and dysfunction

CRPS Type Two (Causalgia)†

1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve
2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

CRPS, Complex regional pain syndrome.
*Criteria two to four must be satisfied.
†All three criteria must be satisfied.

questions about the pathophysiology of this syndrome are still unanswered, three main principles remain at the core of CRPS: abnormalities in both somatosensory and sensory pathways and sympathetic nervous system involvement.

Somatosensory Abnormalities

Inciting injury to either the upper or lower extremity is an important trigger of CRPS. Studies have shown that changes in cutaneous innervation of the injured extremities occur even when no nerve injury is found. Albrecht et al. performed a study where skin biopsy samples were obtained from the affected limbs of patients with CRPS type one. A lower density of C and A fibers were found in the affected limbs than in the unaffected limbs, which led to sensory deficits in the affected limbs.[7] Brain plasticity is another important factor found to be associated with somatosensory abnormalities. Data suggest that patients with CRPS have decreased activity in the somatosensory cortex of the affected side.[8] These patients also tend to have tactile mislocation because of somatotopic reorganization, which was found to be directly correlated with hyperalgesia.[9] Changes occurring within the primary somato-

sensory (SI) cortex are dependent on pain and have been shown to be reversible after recovery from the pain.[10] Recently, a study published by Azqueta-Gavaldon et al. where 20 patients with sensory and motor deficits attributed to chronic CRPS (> six months of pain) underwent a battery of tests including functional magnetic resonance imaging, showed that patients with sensory and motor deficits had bilateral decreases in gray matter in the putamen. They theorize that putamen alterations may explain the pain and motor impairment seen in patients with chronic CRPS.[11]

Sensory Pathways (Central Nervous System Sensitization, Peripheral Sensitization)

Central sensitization occurs when pain perception increases because of the constant firing of painful stimuli to the central nervous system. Neuropeptides such as substance P and bradykinin are released in response to nociceptive stimuli and activate *N*-methyl-D-aspartate (NMDA) receptors, leading to hyperalgesia and allodynia.[12] Chronic exposure to these neuropeptides may influence and remodel normal neuroanatomy. Glial cells (namely microglia and astrocytes) are immunocompetent CNS cells that are activated after tissue injury. In a cadaveric study of an individual with CRPS comparing spinal cord anatomy to four control cadavers, significant posterior horn cell loss along with microglial and astrocyte activation was found at the level of the original injury and entire spinal cord.[13]

Peripheral sensitization is the counterpart of central sensitization. When a nerve injury occurs, multiple pro-inflammatory factors such as glial cell activation, substance P, bradykinin, tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), prostaglandin E_2, and nerve growth factor are activated, which results in increased nociceptive sensitivity and a decreased threshold for the firing of nociceptive stimuli.[14] A study where immunoglobulin G (IgG) from patients with chronic CRPS was injected into mice showed increased edema and paw hyperalgesia with concomitant sustained microglial and astrocyte activation in the spinal cord dorsal horn and pain-related regions of the brain. Furthermore, this was found to be IL-1β mediated as IL-1 receptor antagonists, and IL-1β floxed mice prevented these changes when exposed to IgG of CRPS patients.[15]

Together, central and peripheral sensitization results in the allodynia and hyperesthesia seen in patients with CRPS. There are other important factors in the inflammatory pathway, such as the role of nuclear factor kappa B (NFκB) upstream in the pro-inflammatory pathway observed in animal studies.[16] To date, anatomic, biomolecular, and immunohistologic studies such as those mentioned above illustrated the multifactorial influences in the development of central and peripheral sensitization of this disease along with their effect on neuroanatomy.

Neuroinflammation

An emerging hypothesis for the mechanism for CRPS development is neurogenic inflammation. As mentioned previously, many pro-inflammatory factors are released during nerve injury, evidenced in patients and animal models. This early stage of CRPS ("warm phase") results in vascular symptoms, trophic changes, and pain mediated by neuropeptides with resultant production of high levels of cytokines, nerve growth factors, and mast cells.[17] Studies on IL-6 and TNFα levels in patients with CRPS have shown elevated levels in blisters and skin that decrease once the patient's condition has become chronic.[18–20] Dendritic cells whose roles include activating helper T cells have been hypothesized as the primary mediator for neuroinflammation. [21] A study by Russo et al. utilizing mass cytometry immunophenotyping found that in 14 patients with Budapest criteria supported clinically diagnosed CRPS showed an increased level of central memory CD4 and CD8 T cells implicating a possible role of antigen mediated T-lymphocyte response in the development of CRPS.[22] Although further studies are needed to further validate this pathway, it is possible that neuroinflammation itself plays a role in the evolution of this condition.

Altered Sympathetic Nervous System Function

Involvement of the sympathetic nervous system is thought to be responsible for the limbs in patients with CRPS becoming cool, blue, and painful secondary to vasoconstriction because of excessive outflow from the sympathetic nervous system. In an animal study, rats with chronic post ischemic pain that had norepinephrine injected into their hind paws experienced increased nociceptive firing, supporting the notion that pain can be sympathetically maintained.[23] Interestingly, norepinephrine levels were found to be lower in the affected extremity than the normal contralateral extremity in patients with chronic CRPS. Several studies evaluating the effect of adrenergic receptor stimulation on the vasculature in patients with CRPS have indicated an increased response to an adrenergic stimulus.[24] However, this provides little evidence in support of sympathetic maintenance of CRPS pain.

Coupling of sympathetic neurons may occur not only to nociceptive afferents but also to non-nociceptive mechanosensitive or cold-sensitive neurons. Sympathetic afferent coupling, considered the cause of sympathetically maintained pain, occurs in cutaneous and deep somatic tissues, but during the acute event of CRPS, the deep somatic tissues are of greater importance.[25] Although coupling occurs in some patients with CRPS, a subset of patients with clinically identical CRPS have sympathetically independent pain. These patients exhibit little to no response to sympathetic blockade either pharmacologically with phentolamine or via interventional blockade of the sympathetic ganglia.

Epidemiology

Multiple studies of CRPS type one have shown that the male-to-female ratio ranges between 1:2 and 1:4, thus suggesting that females are at higher risk for the development of the syndrome.[26,27] However, the male-to-female ratio for most other pain syndromes is similar. A retrospective, cross-sectional analysis study showed that the male-to-female ratio was 1:4 and that the most common initiating events were bone fractures, sprains, and trauma.[27] In a prospective study, it was found that CRPS incidence four months after a wrist fracture was 3.8%. This group generated a prediction rule to identify high risk patients based on a 25 min assessment evaluating pain, response time, dysynchiria, and swelling one week after wrist fracture. This study found that a pain score of ≥ five within the first week of injury was nearly as accurate as performing the 25 min assessment in identifying wrist fracture patients at high risk for developing CRPS.[28]

Outcomes of the disease tended to be worse in patients with upper extremity injuries than in those with lower extremity injuries, injuries other than fractures, and "cold" (commonly chronic) CRPS rather than "warm" (acute) CRPS.[16] Other risk factors that contribute to the development of CRPS are age, workplace, concomitant use of angiotensin-converting enzyme (ACE) inhibitors, history of migraines, history of asthma, and type of injury.[29] The average age of patients ranges between 16 and 79 (median range, 41.6), with a higher incidence in the older population. Patients with motor nerve damage were found to be at higher risk for CRPS

than those with sensory nerve damage. Fracture has been reported to be the most common initiating injury.[30] The incidence of job-related injuries leading to CRPS was as high as 76%,[31] which may indicate a psychosocial or secondary gain component in reporting of this pain. Studies report that CRPS develops in patients with a family history of CRPS at a higher incidence and younger age, suggesting that CRPS may have a genetic component.[32] Another study showed that siblings of patients in whom CRPS developed before 50 years of age had a three-fold increased risk for development of the syndrome.[33] Psychological factors such as depression, personality disorders, and anxiety have no correlation with CRPS patients, suggesting no specific type of CRPS personality.[34]

Clinical Features

The pain must be greater in proportion to the inciting event. There must be at least one symptom in three of the following four categories: sensory (hyperesthesia/allodynia), vasomotor (changes in temperature or sweating in the affected limb than the normal limb), sudomotor/edema, and motor/trophic (demonstration of weakness, decreased range of motion, or trophic changes in hair, nails, or skin). At least one sign must be present at the time of evaluation in two or more of these four categories: sensory, vasomotor, sudomotor/edema, and motor/trophic. There must be no other diagnosis that better explains the patient's signs and symptoms.[29] This differs from the criteria proposed in 1993 by the IASP (see Box 34.3). A recent study in which the validity of CRPS was evaluated by comparing the Budapest criteria in patients with CRPS and those with neuropathy showed that the IASP criteria had a sensitivity of 1.0 and a specificity of 0.4, and the Budapest criteria had a clinical sensitivity of 0.99 and a specificity of 0.68.[35] The newly revised criteria are also divided into clinical and research. The research criteria contain more inclusions, which allows a specificity of 0.96.[36]

The current IASP taxonomy also divides CRPS into CRPS one (formerly known as reflex sympathetic dystrophy) and CRPS two (formerly known as causalgia).[29] The distinction between CRPS one and two is the presence of a definable nerve lesion in patients with CRPS two.[37] The signs and symptoms for both conditions are clinically indistinguishable and include sensory changes (allodynia, hyperalgesia, and hypoalgesia), edema, temperature abnormalities, and changes in sweating (see Box 34.3). Pain is the principal feature in both CRPS one and CRPS two. In patients with CRPS, the associated clinical signs are typically out of proportion to the inciting injury. Patients describe a burning, deep-seated ache that may be shooting in nature and associated with allodynia or hyperalgesia.[38] Pain occurs in 81.1% of patients meeting the CRPS criteria.[5] Patients also frequently complain of sensory abnormalities such as hyperesthesia in response to the typical mechanical stimuli encountered in day-to-day activities (such as dressing) involving the affected limb.

In CRPS two (i.e. CRPS with associated major nerve injury), patients often report hyperesthesia around the injured nerve in addition to electric shock-like sensations, shooting pain, and allodynia. Symptoms indicative of vasomotor autonomic abnormalities (including color changes) occurred in 86.9% of patients; temperature instability occurred in 78.7%. Sudomotor symptoms of hyperhidrosis and hypohidrosis were reported in 52.9%. Trophic changes in skin, nail, or hair patterns were reported in 24.4%, 21.1%, and 18%, respectively. Edema was reported in 79.7%, with decreased range of motion in 80.3% and motor weakness in 74.6%.[5]

Over time, symptom severity changes reflecting stability or progression of disease. In 2010 Harden et al. developed a CRPS symptom severity score (CSS) to help categorize the degree of CRPS for aiding in clinical decision making, which was validated by an international prospective multi-site study.[35,39] In the study, they found that changes in CSS correlated with greater changes in fatigue, pain intensity, social functioning, ability to take physical roles, and overall wellbeing, indicating the possible role of this score in clinical monitoring and research.[39] Eventually, approximately three-quarters of all CRPS cases resolve even without treatment, with the resolution of microvascular signs and symptoms resolving before resolution of pain.[40]

Diagnosis

There is currently no "gold standard" test for the diagnosis of CRPS. A very thorough history and physical examination are essential for evaluation and diagnosis. Patients with this condition will have the signs and symptoms mentioned. Many clinicians utilize the Budapest criteria (Box 34.2) to help diagnose this condition. In 2018, a European Pain Federation Task Force developed standards for diagnosis and treatment of CRPS where they recommended the utilization of the Budapest criteria as the main tool to diagnosis the condition with further diagnostic tests only to exclude other diagnoses.[41]

A physical examination must be performed to establish the sensory, motor, trophic, sudomotor/edema, and autonomic changes. Sensory changes such as allodynia may be evaluated by light touch and the application of warm/cold temperature to the affected area. Autonomic dysfunction may be confirmed by the presence of asymmetry in temperature and color. Trophic changes may be manifested as changes in skin, nails, and hair in the affected limb. Motor activity may be evaluated by examining motor strength and range of motion. Sudomotor/edema changes may be assessed by dragging a smooth object over the affected and unaffected limb, with the wetter limb allowing a smoother drag than the drier limb.[42] Common diagnostic tools used for diagnosis, characterizing, and monitoring of CRPS include quantitative sensory testing, tests of autonomic function, and imaging for trophic changes.

Quantitative Sensory Testing (QST)

QST is a noninvasive means to evaluate sensory and pain perception to classify pain but cannot be used as the sole method to diagnose a particular pain pathology. There is variability in the ability to reproduce results, and as such, the precision and accuracy of this modality are still up for debate.[43] Such testing includes the use of standardized psychophysical tests of the sensory and motor systems, thermal sensation, thermal pain, and vibratory thresholds to assess the function of myelinated small fiber and unmyelinated small fiber afferents. Patients with CRPS may have impaired paradoxical heat sensations, mechanical detection thresholds, mechanical pain thresholds to pinprick stimuli and blunt pressure, allodynia, and pain summation with the use of continuous pinprick stimuli.[44] There is currently no definitive diagnostic sensory pattern in patients with CRPS, but this test can aid in distinguishing other neuropathies from CRPS.[45,46]

Tests of Autonomic Function

Thermoregulation and sudomotor regulation are the main systems tested in patients with CRPS for disorders in autonomic function. Thermoregulation is tested by using the thermoregulatory sweat test (TST) and infrared thermography or thermometry. The TST

assesses calorimetric precipitation from a specific region of the body by adding a solution that changes color when enough heat is generated to produce sweat.[47] Infrared thermography is direct visualization of the change in temperature of the affected site, and in infrared thermometry, a device is used to measure temperature through the detection of infrared energy. Changes in temperature in patients with CRPS versus those with other types of pain had a sensitivity of 76% and a specificity of 94%.[48] Sudomotor regulation is tested by using the quantitative sudomotor axon reflex test (QSART), which measures sweat output from various regions of the skin. However, a recent retrospective review of patients who underwent QSART was found to have a sensitivity of 67.6% and specificity of 40.6%, with a not statistically significant odds ratio of 1.43.[49]

Trophic Changes

Three-phase bone scintigraphy (TPBS) is a very valuable test for the detection of CRPS. Although joint and bone alterations are not part of the IASP inclusion criteria, they are very important in the outcome of the syndrome.[25] TPBS detects alterations in periarticular bone metabolism, particularly increased bone metabolism, by detecting increase uptake of a periarticular tracer, which occurs predominantly within the first year. TPBS is low in sensitivity but high in specificity.[50] Furthermore, TPBS may have a role in monitoring treatment effectiveness for CRPS as well, possibly predicting disease response to ketamine treatment.[51,52] Magnetic resonance imaging of the affected limb has also been used for detection of CRPS but has high sensitivity (97%) and low specificity (17%).[53]

Treatment

Management of CRPS has been complicated by scant knowledge of the cause of the disease, which has resulted in few targeted therapies. Most of the medications initiated as first line therapy have been investigated for other non-CRPS neuropathic pain conditions and then applied to the treatment of CRPS, with mixed success. The historical approach to therapy for CRPS remains a multimodal, multi-disciplinary methodology. The predominant therapeutic modalities for the care of CRPS patients include physical therapy, pharmacologic agents, and interventional procedures.

Physical and Occupational Therapy

Physical and occupational therapy for restoration of function and improvement of limbs affected by CRPS has been studied widely. Physical exercises such as isometric strengthening, active range of motion, myofascial release, and stress loading are all tools that aid in restoring the functional capacity of the affected limb.[54] A 2019 multi-disciplinary study utilizing physical therapy modalities (graded motor imagery and physiotherapy exercises) along with psychological treatment, memantine, and morphine treatment was successful in reducing some of the CRPS symptoms.[55]

Other methods of therapy are currently under study. In a large controlled study in which tactile acuity and pain on the application of a tactile stimulus were measured in patients with CRPS, and mirror images were used to show the reflection of the unaffected limb during the stimulus, a decreased two-point discrimination threshold and decreased pain acuity were observed.[56] This suggests that therapies that improve functional restoration of the affected limb (including mirror therapy) may improve the outcome of CRPS.[57] However, evidence for other forms of physiotherapy for the management of CRPS I and II is unclear.[58] Despite ongoing studies and modeling, an optimal clinical physiotherapy algorithm to treat this condition has yet to be validated.[59]

Pharmacologic Therapy

Membrane Stabilizers

Medications such as gabapentin and pregabalin have been shown to be effective in relieving neuropathic pain.[60,61] CRPS is considered neuropathic pain, and gabapentin is presumed to be effective in treating it, yet there are very limited studies showing its specific efficacy for CRPS. In a randomized, double blind, placebo controlled crossover study in which patients were treated for two three week periods with two weeks in between, gabapentin had minimal effect on pain, but it significantly reduced patients' sensory deficits.[62] In a case report of a 15-year-old female with left arm CRPS one, pregabalin was successful in the management of her pain after she failed treatment with gabapentin, selective serotonin anti-depressants, and stellate ganglion block.[63] Although there is no clear evidence of efficacy for gabapentin, these neuroleptic medications are the first line therapy for neuropathic pain and are thus considered first line therapy for CRPS.

Corticosteroids

A large part of the pathophysiology in CRPS is the acute inflammatory process that occurs after an inciting event (see "Pathophysiology"). Because of this inflammatory course, corticosteroids have been used for treatment. In a 2006 randomized controlled trial comparing prednisolone with piroxicam, patients were given either medication for one month, and their shoulder-hand syndrome scores (measuring pain, distal edema, passive humeral abduction, and external rotation) were determined. In the prednisolone group, 83.3% showed improvement, and in the piroxicam group, only 16.7% improved. The shoulder-hand syndrome score in the steroid group was significantly lower than that in the piroxicam group.[64] Other studies have shown that continuation of prednisolone treatment (two months) after an initial one month high-dose (40 mg) taper was successful in reducing post stroke CRPS one patients.[65] Short term steroid use was further found to normalize microcirculation in response to remote ischemic conditioning (RIC, a non-damaging method to induce ischemia to an extremity) in CRPS patients (typically RIC causes an increased O_2 extraction and decreased blood flow) implicating the anti-inflammatory role of steroids in CRPS.[66]

Anti-depressants

These drugs have not been studied for use specifically with CRPS, but they have been widely studied for the control of neuropathic pain, and because CRPS is considered neuropathic pain, they are used in pain management. Anti-depressants such as tricyclic anti-depressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) have been used to control neuropathic pain effectively. In a recent Cochrane review, TCAs were found to be effective in treating neuropathy, with a number needed to treat (NNT) of 3.6 and a relative risk (RR) of 2.1. Venlafaxine, an SSNRI, was also found to be effective, with an NNT of 3.1 and RR of 2.2.[67] Further studies to investigate the drugs' ability to specifically target CRPS are warranted. A recent study showed that the combination of gabapentin and nortriptyline was a more effective therapy than either medication alone for neuropathic pain (including CRPS).[68] In children with CRPS, a randomized controlled trial comparing amitriptyline to gabapentin revealed no statistical difference between the efficacy of both medications in successfully decreasing pain intensity scores.[69]

Opioids

Studies on the effects of opioids directly on CRPS are lacking, although some have shown opioids to improve neuropathic pain when used in high doses.[70] However, a double blind, placebo controlled trial studying the efficacy of sustained-release morphine in CRPS patients for a total treatment of eight days showed that it was ineffective in decreasing pain, but the study had many limitations.[71] In 2016, a Cochrane review evaluating fentanyl use for the treatment of neuropathic pain including CRPS and PHN showed that there was insufficient evidence to support or refute the use of the medication in those conditions.[72] Substantial challenges to using opioid therapy for nonmalignant pain include nausea, constipation, cognitive impairment, tolerance, and hyperalgesia.[73,74] Therefore it should be used only until other therapies can be initiated. Studies of these medications in the CRPS population are lacking, and more is needed to demonstrate the efficacy of opioids.

Ketamine

Ketamine is an NMDA receptor antagonist. The NMDA receptor is a major part of the central sensitization that occurs in patients with CRPS (see "Pathophysiology"). Ketamine can be administered topically, orally, intranasally, or parentally in subanesthetic (analgesic) doses or in high doses to produce ketamine coma. Its role in medicine has expanded from anesthetic uses to include treatment of pain (acute and chronic), headaches, seizures, and depression.[75] A double blind, randomized, placebo controlled, parallel-group trial studying the effects of subanesthetic intravenous dosing of ketamine for four days in CRPS patients showed decreased pain levels, but the pain progressively increased from the first week after infusion to the 12th week. In patients undergoing ketamine infusion, minor and rare side effects such as nausea, vomiting, and psychomimetic effects developed.[76] In another nonrandomized open-label trial in which chronic CRPS patients refractory to standard therapies were treated with anesthetic doses of ketamine for five days, the pain improved significantly for six months, but 79.3% relapsed back to baseline after the six months.[77] A 2018 meta-analysis of 15 studies where ketamine was used for the treatment of CRPS included 15 randomized controlled or cohort studies revealing an immediate pain relief rate of 69% with a 58% pain relief rate at one to three months follow up.[78] The topical form of ketamine has also been shown to decrease allodynia and hyperalgesia in response to pinprick stimuli,[79] but this has not been well validated.

Bisphosphonates

Bone resorption at the site of inflammation in the affected limb contributes to the pain in CRPS. The use of bisphosphonates to decrease osteoclast overactivity has shown promise in its pain-reducing effects. In an eight week randomized, double blind, placebo controlled study, alendronate was used in patients with posttraumatic CRPS type one. This drug improved spontaneous pain, tolerance to pressure, and extremity range of motion.[80] However, other trials have shown no reduction in CRPS-related pain.

A 2013 Cochrane review evaluating interventions for pain treatment of CRPS patients from six Cochrane reviews and 13 non-Cochrane reviews showed low quality evidence that bisphosphonates may be beneficial for pain management.[81] A later review in 2018 of four moderate to good quality trials were analyzed, which revealed significantly lower short term (30–40 days) and medium term (two to three months) visual analog scale (VAS) reduction in patients on bisphosphonates for the treatment of CRPS one.[82] However, a higher percentage (35.5% vs. 16.4%) of adverse events occurred compared to placebo with a RR of 2.1, and the number needed to harm of 4.6 was reported, although no serious side effects were observed.[83] Because of the success of bisphosphonates in the management of acute phase CRPS type one, it was theorized that bone tissue involvement (through the release of inflammatory cytokines and effects on microvascular remodeling) plays an integral role in the early stages of CRPS one development.[84]

Interventional Treatment

Sympathetic Nerve Block

The most common sympathetic nerve blocks are the stellate ganglion and lumbar sympathetic blocks for the treatment of CRPS of the upper and lower extremities, respectively. Multiple modalities have been studied for their ability to disrupt the sympathetic pathway through these nerve plexuses, including local anesthetics, chemical neurolysis, and radiofrequency ablation. In a study in which both stellate ganglion and lumbar sympathetic blocks were performed with local anesthetic and normal saline on each subject, it was observed that the decreased pain that each experienced was almost identical, but the duration of decreased pain was longer when patients received the local anesthetic block.[85] In a small randomized study in which radiofrequency neurolysis was compared to chemical neurolysis, the pain decreased from baseline, but no significant difference was seen between the two methods.[86] A retrospective review of 287 stellate ganglion blocks for upper extremity CRPS treatment showed an average reduction of > three numeric rating scale from baseline or provoked pain.[87]

Although sympathetic blocks may provide a significant reduction in pain by blocking the sympathetic pathway of the pathophysiologic stages in CRPS, their greatest limitation is that they provide only short term relief in the vast majority of treated patients. This means that patients must continue to frequently undergo sympathetic blocks, which most often places them on maintenance therapy. A 32 question survey evaluating the use of sympathetic blocks for CRPS treatment was distributed nationally with a response from 248 pain physicians. In this group, 44% of providers schedule a sympathetic block at the first clinic visit, with 73% of providers performing one to three consecutive blocks with over 50% of respondents performing repeat injections for patients with at least 50% response from the prior injection.[88] This form of therapy should be performed to provide enough pain relief so that patients are able to perform physical therapy exercises for functional restoration and multi-disciplinary therapy, but not as a sole therapeutic modality.

Neuromodulation

Neuromodulation has implemented itself in the treatment algorithm of patients with chronic pain, including CRPS, utilizing percutaneous or surgically placed leads in the epidural space implementing electrical dosing via an implantable pulse generator (IPG). Currently, modalities for the treatment of CRPS include dorsal column neuromodulation and dorsal root ganglion (DRG) neuromodulation. In a randomized trial, patients with CRPS were separated into two groups: spinal cord stimulation (SCS) with physical therapy and physical therapy only.[89] This study showed that SCS provided significant improvement in pain for the first two years.[90] Unfortunately, there was no amelioration in quality of life or functionality in the group undergoing SCS with physical therapy, although this study was seriously flawed because of excessive patient dropout.[91] Several studies since have been performed evaluating the efficacy of these techniques in managing CRPS. A systematic review of 19 manuscripts evaluating SCS in

the treatment of CRPS revealed improvement of perceived pain, pain score, and quality of life in patients. However, the results from this review were inconclusive for the role of SCS in improving functional status, psychological status, sleep hygiene, or resolution of the signs of CRPS.[92]

DRG neuromodulation was first evaluated in a multicenter prospective trial for management of chronic pain, including nine patients with CRPS of the lower extremity. Six months after implant, participants had an overall reduction of 58% from baseline.[93] The ACCURATE study was a prospective multicenter randomized controlled trial evaluating the efficacy and safety of DRG neuromodulation in the treatment of CRPS of the lower extremities than tonic dorsal column neuromodulation. The 152 patient study showed that there was a greater percentage (81.2% vs. 55.7%) of patients with >50% pain relief at three months post implant without difference in the incidence of device related or serious adverse events.[94] This finding was further emphasized by the Neuromodulation Appropriateness Consensus Committee (NACC) guidelines for DRG best practices.[95] Though the role of neuromodulation for management of upper extremity CRPS requires further investigation, neuromodulation may be an effective therapy of management of lower extremity CRPS.

Intrathecal Treatments

Baclofen and ziconotide administered intrathecally have been examined for the treatment of CRPS. Baclofen is a γ-aminobutyric acid receptor agonist. It is used as a muscle relaxant and has been indicated for muscle spasticity and dystonia. A single-blind, placebo run-in, dose escalation study of CRPS patients with dystonia showed that intrathecal baclofen was very effective in decreasing dystonia and pain, as well as in improving quality of life, as indicated in a 12-month follow up.[96] Ziconotide is a very potent drug made from the toxin of sea snail venom and works by blocking chemicals that transmit pain signals. Intrathecal administration of this drug has great potential in reducing edema, trophic changes, and pain in these patients.[97] However, it is associated with a nearly 100% side effect profile. Incidentally, a four-year retrospective evaluation of 26 patients with intrathecal pumps for CRPS management revealed that intrathecal narcotics did not reduce the dose of oral narcotics while intrathecal ziconotide may.[98] Other medications trialed with success include clonidine[99] and morphine with bupivacaine.[100] The majority of the literature surrounding the use of intrathecal treatments for CRPS are case reports, and formalized trials are needed to verify the efficacy of these modalities.

Postherpetic Neuralgia

Postherpetic neuralgia is neuropathic pain that arises from herpes zoster (HZ- shingles) in a dermatome distribution. This form of pain is very debilitating and leads to poor quality of life and poor functional status at home and in society. Control of pain is difficult, with multiple interventions being required. There are multiple risk factors for the development of HZ and subsequent PHN. It is essential to understand the risk factors, pathophysiology, and diagnostic approach to PHN to delve into the various pharmacologic and interventional treatments available.

Epidemiology and Risk Factors

Varicella is a viral infection that may lead to varicella zoster (chicken pox) on first exposure and remains in a latent phase for the majority of lifetimes. HZ develops secondary to the reactivation of the varicella virus from its latent state. Varicella virus is kept in a latent state by the body's cell-mediated immunity. When there is a decrease in cell-mediated immunity, the risk for reactivation and subsequent HZ increases. Cell-mediated immunity may decrease with age, HIV infection, cancer, and immunosuppressive therapy as used for transplant patients.[101] The annual incidence of acute herpes zoster is estimated to be 3.4 cases per 1,000 patients with significant increases after the age of 50 years, with an approximate incidence of 11 cases per 1,000 patients by the age of 90 years.[102] A separate study found the incidence as 3.6 cases per 1,000 person-years that was low for patients between age 20–29 years old but increased to 7.1 cases per 1,000 person-years by seventy and 12.0 cases per 1,000 person-years by eight years old.[102]

PHN pain is pain that persists three months after the acute phase of the disease. It is seen in approximately 10%–20% of patients infected with HZ.[103] The incidence of PHN developing from HZ also increases with age, with 80% of cases occurring in patients 50 years or older.[103] Patients older than 70 years with HZ have a 50% risk for the development of PHN; approximately 13% of all patients over 50 years old will develop this condition.[104] PHN rarely develops in patients younger than 40 years. There are many risk factors for the development of PHN, and among them are increased age, greater severity of the rash during the acute phase, female gender, and greater acute pain severity.[105] In an epidemiologic study of patients with PHN in the Ferrara University Dermatology Unit, Italy, from 2000–2008, males had an earlier age at onset than females did, and 72% of the patients were older than 45 years. The most commonly observed sites were ophthalmic in 32%, thoracic in 16.5%, and facial in 16%.[106] The correlation of PHN developing after the first episode of HZ was reviewed in a prospective study in which patients were monitored for 12 months. It was concluded that three months after the appearance of the HZ rash, the risk for the development of PHN was 1.8%. In patients older than 60 years, the risk for the development of PHN and the severity of the pain was higher.[107]

In recent years, the administration of the varicella vaccine has become very popular as PHN cannot be prevented once a patient has developed HZ.[108] Some data suggest that these vaccines may lead to an increase in the incidence of HZ secondary to a reduced opportunity for subclinical boosting, which results in an extreme reduction in the incidence of varicella from the immunizations.[109] However, the administration of the zoster vaccine has been proven to decrease the incidence of HZ and PHN. In a randomized, double blind, placebo controlled trial of the zoster vaccine, the incidence of PHN decreased by 66.5% ($P < 0.001$), and the incidence of HZ decreased by 51.3% ($P < 0.001$).[110] In a population-based database review of post-vaccination incidence of HZ after starting a varicella vaccination program in Ontario the rate of HZ increased, incidence decreased by 29% in children, and hospitalization visits decreased because of HZ by 53%.[111]

Original versions of the vaccine contained live attenuated varicella zoster virus. The efficacy waned over time (six to eight years), but an immune boost can be provided with revaccination ten years after the initial vaccination. In 2017, a new recombinant glycoprotein E adjuvant vaccine was approved and available for use in the United States with increased efficacy and less decline over time than the live attenuated virus.[108] The recombinant vaccine was found to be significantly more efficacious in reducing HZ and PHN incidence in adults ≥60 years old than the live attenuated vaccine.[112]

Pathophysiology

Varicella zoster is the primary infection that leads to chicken pox. After the primary infection, the virus remains dormant within one of the sensory nerve ganglia, the most common of which are the trigeminal and thoracic ganglia; these are also the sites where most of the cutaneous dermatomes are involved. The cell-mediated immune system keeps the virus dormant in the latent phase. Progression from the latent phase to reactivation of the virus leads to the development of HZ and subsequently PHN in some patients.[113] During the reactivation phase of varicella zoster virus (VZV), destruction of neurons and satellite cells occurs because this is the site of replication for the virus.[114] VZV traveling along the affected sensory nerves leads to evasion of the host immune system and spreads from cell to cell until its characteristic unilateral dermatome rash is produced. The spread of the virus and its destruction of neurons occurs before the development of the rash.[115] Studies in postmortem patients have led to the conclusion that reactivation and replication of VZV result in inflammatory changes within the sensory neurons that it disturbs, which causes pain. This mechanism may help explain the findings of loss of cells, myelin, and axons, fibrosis of the affected ganglion, and atrophy of the dorsal horn in postmortem patients.[116]

The previously mentioned mechanism contributes to the two primary pathophysiologic mechanisms of PHN pain: sensitization (hyperexcitability) and deafferentation.[117] These mechanisms describe not only peripheral nerve pain but also central nerve pain.[118] Following nerve injury, nociceptive receptors in the peripheral and central nervous systems become sensitized, so the threshold for the firing of action potentials after a certain stimulus is lowered. This causes the nerve to become hyperexcitable and leads to allodynia without sensory loss.[117] Deafferentation pain arises from the neuronal destruction and loss of afferent neurons that occur after the virus reactivates and subsequently produces the inflammatory response within the affected nerve. The loss of afferent neurons leads to spontaneous activity centrally, which results in pain in areas where there is sensory loss. Neural sprouting is initiated in an attempt to reconnect the former C-fiber receptors, a process that leads to hyperalgesia with allodynia.[117] The sympathetic nervous system is also thought to play a role in PHN by stimulating a vasoconstrictive response during the inflammatory process that results in decreased intraneural blood flow, hypoxia, and endoneurial edema.[119] Typically, patients will report three types of pain, including constant pain without stimulus, intermittent pain without stimulus, and pain with a stimulus that is disproportionate to the stimulus.[118]

Diagnosis

Postherpetic neuropathy is principally a clinical diagnosis. The typical clinical scenario involves a patient complaining of persistent pain that is within a certain dermatome and affects the region that the dermatome innervates in a unilateral fashion.[120] The acute phase of HZ is characterized as a maculopapular vesicular rash that crusts over after one to two weeks and results in a burning sensation, hyperesthesia, itching, and severe pain. Prodromal symptoms that may occur one to five days before the rash include headache, fever, malaise, abnormal skin sensation, and photophobia. PHN may occur two weeks after the presence of HZ and is the chronic form of the disease. This is a very debilitating pain that consists of burning, dysesthesia, pruritus, and allodynia or paresthesia of the affected dermatomal region. The pain usually decreases or resolves within six months after exposure, but in some cases, it may last years.[121]

A detailed physical exam is often helpful in the diagnosis as patients will have sensory abnormalities in the area involved, including allodynia, hyperalgesia, or dysesthesia to touch. Furthermore, thermal stimulus and vibrational stimulus may elicit these sensory abnormalities as well.[118] Furthermore, QST may be a useful tool in helping further assess the functional status of the somatosensory system.[122]

Treatment

Therapy for HZ can be separated into the acute phase (shingles) and the chronic phase (PHN). In the acute phase of the disease process, the first line medications that have proved to significantly decrease the length of disease are antiviral medications such as famciclovir and valacyclovir. Three randomized controlled trials that measured the efficacy of these agents when initiated within the first 72 hours of disease onset concluded that they were all effective in increasing the rate of healing and decreasing pain.[123–125] Another study showed that valacyclovir resulted in faster complete resolution than acyclovir did (44 vs. 51 days, respectively).[126] In addition, a study comparing famciclovir with valacyclovir showed no statistically significant difference.[123] A Cochrane review of antivirals in the prevention of PHN showed high quality evidence that oral acyclovir does not reduce the incidence of PHN significantly. Unfortunately, data on the administration of antiviral medications aside from acyclovir for the prevention of PHN are inconsistent.[127] When deciding which agent to use, it is important to consider the amount of administration and cost (Table 34.1).

Other medications that may be used to control the pain of acute HZ are acetaminophen, nonsteroidal anti-inflammatory agents, tramadol, and opioids.[101] Studies and randomized trials comparing

TABLE 34.1 Antiviral Medications for Acute Herpes Zoster

Medications	Recommended Dosages	Side Effects	Prices
Acyclovir	800 mg five times a day for seven to ten days	Nausea, vomiting, diarrhea, constipation, decreased appetite, headache, joint pain	$24.95 for 30 400-mg tablets
Valacyclovir	1000 mg three times a day for seven days	Nausea, vomiting, diarrhea, constipation, abdominal pain and cramping, headache, tremors	$173.92 for 30 1-g tablets
Famciclovir	500 mg three times a day for seven days	Headache, nausea, vomiting, fatigue, pruritus	$166.38 for 21 500-mg tablets

opioids, TCAs, and membrane stabilizers for treatment of acute pain from HZ are lacking, but they are still recommended as adjunctive therapy for refractory severe pain.[101] The addition of corticosteroids with antiviral medications has proved effective in relieving the intensity of the pain of shingles, but not the duration of the disease process.[128] Furthermore, corticosteroid administration did not aid in preventing the development of PHN, as shown in a Cochrane review study.[129]

Interventional therapy for the treatment of acute HZ has proved effective in relieving the pain but not consistent in preventing the development of PHN. A randomized trial in which patients older than 50 years with HZ were given standard therapy versus standard therapy and one epidural injection of methylprednisolone, 80 mg, with bupivacaine, 10 mg, showed that in one month, patients in the epidural injection group experienced a significant reduction in pain.[130] A randomized prospective study was performed comparing interlaminar and transforaminal steroid injections for management of acute phase HZ found similar VAS, Short Form (36) Health Survey Physical Component Summary (SF 36 PCS), and Short Form (36) Health Survey Mental Component Summary (SF 36 MCS) scores with no difference in analgesic effects one or three months between the two groups.[131] An alternative method for acute HZ treatment with subcutaneous injection of triamcinolone with lidocaine was reported with improvement in pain at three months post infection than standard antiviral therapy with analgesics.[132] Further studies are needed to validate this modality of acute HZ treatment.

Analgesic Therapy

PHN is a neuropathic pain historically refractory to many forms of therapy. PHN therapies have been separated into analgesic medications (e.g. topical, membrane stabilizers, opioids), interventional procedures (such as sympathetic blocks, intrathecal injections, or surgical interventions), and preventative therapy with the zoster vaccine. Nontraditional PHN therapies such as cognitive and physical therapy have also proved beneficial. As with most other chronic pain disorders, a multimodal therapeutic plan leads to an optimal chance of success.

Medications such as gabapentin, pregabalin, tramadol, and topical lidocaine are considered first line treatments because they have been shown to be most well tolerated by the (commonly elderly) patient population. Other medications shown to help patients with PHN are TCAs and SSNRIs, opioids, and topical capsaicin cream (Table 34.2). The therapeutic modality chosen is patient specific and depends on a thorough history and physical examination.

Topical Medication

A 5% lidocaine patch and 4%–10% lidocaine cream are widely used topical forms. A randomized, two-treatment period, vehicle-controlled, crossover study showed that a lidocaine patch is effective in controlling PHN pain from allodynia. At the end of the study, 78.1% of subjects enjoyed the lidocaine patch treatment phase, and only 9% liked the placebo patch treatment phase.[133,134] The lidocaine patch is also very safe because of minimal systemic absorption. It is also used safely with other medications based on studies showing no significant drug-drug interaction. The most common side effect reported has been mild skin irritation.[135] The NNT has been quoted as 2.0 with 95% confidence intervals (CI) 1.4–3.3.[136]

Topical capsaicin in cream or high-concentration patch form has shown promise in treating PHN pain. The first application of the cream leads to exacerbation of the burning sensation, but with time, application leads to desensitization of the nerve root endings and decreases the hyperalgesia. In a four week, double blind study, patients were randomized to receive a high-concentration topical capsaicin patch or placebo. The study showed that the high-strength capsaicin patch relieved pain in 64% of patients at the six week mark than 25% taking placebo.[137] The NNT has been quoted as 3.3 with 95% CI 2.3–5.8 for the cream and NNT 11.0 with 95% CI 6.1–62.0 for the patch.[136]

Anti-convulsants

Gabapentin has been used widely as a first line therapeutic agent for PHN. A quantitative systematic review of randomized controlled trials indicated that the pooled NNT for gabapentin was approximately 4.4.[138] Another study, a randomized, double blind, parallel-group trial of nine weeks' duration, showed that gabapentin was

TABLE 34.2 Efficacy and Side Effects of Analgesic Medications for Post-herpetic Neuropathy

Medications	Number Needed to Treat (NNT)	Side Effects
Anti-convulsants		
Gabapentin	4.3	Diarrhea, dizziness, drowsiness, dry mouth, tiredness, somnolence
Pregabalin	4.9	Blurred vision, changes in sexual function, constipation, dizziness, drowsiness, dry mouth
Topical		
Lidocaine	2	Mild skin irritation
Capsaicin	3.6	Major skin irritation and burning
Tricyclic anti-depressants	2.64	Dizziness, drowsiness, dry mouth, headache, impotence, nausea, nightmares, pupil dilation, sensitivity to sunlight, sweating, tiredness
Opioids		
Tramadol	4.76	Constipation, dependence, dizziness, drowsiness, increased sweating, loss of appetite, nausea
Oxycodone	2.64	Constipation, dependence, dizziness, drowsiness, increased sweating, loss of appetite, nausea
Morphine	2.64	Constipation, dependence, dizziness, drowsiness, increased sweating, loss of appetite, nausea

just as effective as nortriptyline but was tolerated better. After nine weeks of gabapentin treatment, the pain score declined by 43%, and sleeping improved by 52%.[139] The dosage may be titrated up to effect to 1800 mg/day to a maximum of 3600 mg/day.[140] Pregabalin has an identical site of action as gabapentin and is as efficacious in the treatment of PHN. It has the drawback of being on patent (and therefore more expensive) but can be better tolerated by patients because of its greater bioavailability, which results in twice a day dosing compared to the three times daily dosing required for gabapentin.[141] Pregabalin has a similar NNT of 4.2 with 95% CI 3.4–5.4 with a similar side effect profile as gabapentin, including sedation, dizziness, and peripheral edema.[136]

Anti-depressants

TCA medications have been the first line therapy for neuropathic pain. In a 2006 randomized, double blind, parallel-group trial of nine weeks' duration, patients with PHN who received nortriptyline had a 47.6% reduction in pain with sleeping scores improved from baseline.[139] A quantitative systematic review of analgesic therapy for PHN noted a significant analgesic benefit with TCAs for the treatment of PHN pain, with the pooled data showing an NNT of 2.6 (95% CI 2.1–3.5).[138] The efficacy of amitriptyline in providing relief of pain in patients with PHN was studied by comparing nortriptyline with amitriptyline. The results showed that both these drugs provided adequate pain relief in 67% of patients. Although they are both equally effective, patients tolerated nortriptyline better because of its fewer side effects.[142]

Venlafaxine is another anti-depressant medication with the potential for the management of neuropathic pain, including PHN. It is classified as an SSNRI and provides relief of neuropathic pain by increasing the amount of serotonin and norepinephrine and inhibiting their reuptake. This drug has been shown to have fewer side effects than TCAs.[143] Venlafaxine must be used in doses exceeding a total daily dose of 200 mg/day to inhibit norepinephrine reuptake; doses below this level will only inhibit serotonin reuptake and have no analgesic benefit. A 2015 Cochrane review evaluated six double-blinded randomized controlled trials that revealed little compelling evidence to support the use of venlafaxine for neuropathic pain. However, there was some lower quality studies that implicated benefit, and the authors of the review do not recommend revising prescribing guidelines to promote venlafaxine use, given the number of effective medications available to treat neuropathic pain.[144] This may be because of venlafaxine's side effects, including hypertension, exacerbation of seizures, and mania.

Opioid Medications

Although opioids are considered effective in overall pain management, their efficacy in controlling neuropathic pain is still controversial. In a double blind, crossover, four week study of sustained-release oxycodone, 20–60 mg, for moderate to severe pain in patients with PHN, the response rate for pain relief was 58% versus 18% for placebo.[145] Another study reported that the administration of 10 mg oxycodone to a patient already taking pregabalin did not enhance the pain relief obtained,[145] demonstrating that oxycodone at low doses is not as effective as the administration at higher doses. Morphine was also found to be beneficial in managing the pain of PHN. It was shown that a combination of morphine and gabapentin improved neuropathic pain in patients with PHN more than did either of them alone.[146] These data suggest that opioids at high doses are of therapeutic value in relieving pain in patients with PHN. The NNT for morphine was quoted as 2.8 with 95% CI 2.0–4.6, while the NNT for oxycodone was 2.5 with 95% CI 1.7–4.4.[136]

Tramadol

Tramadol is a weak μ-receptor agonist medication with properties that increase the release of serotonin and inhibition of norepinephrine reuptake. This medication has been effective in treating neuropathic pain with an NNT of 4.8.[147] In a multicenter, randomized, double blind, parallel-group study involving 127 outpatients treated with tramadol or placebo for six weeks, the tramadol group showed significantly reduced pain than the placebo group. Quality of life in the tramadol group was also improved.[147]

Combination Therapy

Many studies have combined medications to achieve the greatest efficacy with the least dosage and increased tolerability of the medications. In a double blind, double-dummy, crossover trial in which patients with neuropathic pain took gabapentin or nortriptyline as monotherapy or combination therapy, combination therapy was shown to be better than monotherapy. However, each medication was effective in relieving neuropathic pain.[68] The combination of gabapentin and morphine has also been widely researched. Gabapentin combined with morphine was more effective than either medication alone.[146]

Interventional Therapy

Interventional therapy for the pain of PHN includes nerve blocks, intrathecal injections, and SCS. Interventional therapies are not considered a first line choice, but they should be considered in a multimodal management approach for PHN treatment.

Sympathetic Nerve Blocks

The role of sympathetic nerve blocks is to provide relief of pain during the development of HZ, provide relief of PHN pain, and prevent the development of PHN from HZ. Unfortunately, most of the data attempting to prove the efficacy of sympathetic nerve blocks in these three main roles come from retrospective studies and are limited. Thus the use of sympathetic nerve blocks remains controversial. In a small, randomized study based on retrospective data in which bupivacaine was compared to the saline solution, there was evidence of the reduced duration of acute HZ pain in patients with sympathetic nerve blocks.[119] Another retrospective study concluded that sympathetic nerve blocks provided temporary short term pain relief in 41%–50% of patients with PHN.[148] A study comparing sympathetic nerve blocks and lidocaine patches for the treatment of PHN revealed similar rates of failure (18.9% vs. 27.1%, respectively) with similar average Numerical Rating Scale (NRS) change (5.88 vs. 5.01) but a significant proportion of patients remaining pain free eight weeks after treatment in those treated with sympathetic blocks than those with lidocaine patches (34.4% vs. 13.5%).[149]

Neuraxial Blocks

Epidural injections, paravertebral injections, and intrathecal steroid injections have all been used for temporary relief of pain from PHN, with successful short term results. Epidural steroid injections have been proved to effectively reduce pain in the acute phase of PHN, but most research has focused on its effects in preventing the progression of HZ to PHN. In a study performed in Italy, 600 patients older than 55 years with HZ were administered bupivacaine and methylprednisolone through an epidural catheter versus intravenous administration of prednisolone and

acyclovir until they were pain free. After one year, the incidence of PHN was 22% in patients receiving intravenous prednisolone and acyclovir instead of 1.6% in those receiving bupivacaine and methylprednisolone through an epidural catheter.[150] A retrospective review of PHN patients receiving epidural steroid injections to determine variables to predict the efficacy of injection revealed no demographic characteristics, concurrent medication use, or type of epidural steroid injection were associated with efficacy at two or 12 weeks after the injection.[151]

The efficacy of paravertebral blocks in preventing PHN was assessed in a single-center randomized study of patients with HZ given either the standard therapy of oral antivirals and pain medications or a series of four paravertebral injections with bupivacaine and methylprednisolone besides standard therapy. The study concluded that after 12 months, the incidence of PHN with standard therapy alone was 16% compared to 2% in the paravertebral block group. Although it seems that paravertebral blocks are effective in preventing PHN, larger multicenter trials are still required.[152]

Another promising procedure for the relief of PHN pain is intrathecal methylprednisolone. A study in which 279 patients with intractable PHN pain for more than one year were given either intrathecal methylprednisolone with lidocaine, lidocaine alone, or no therapy concluded that the group receiving methylprednisolone with lidocaine experienced a significant reduction in pain than the groups receiving lidocaine alone or no therapy.[153] Unfortunately, these data have never been replicated, and clinical experience has not corresponded to the positive results that the authors obtained. Further, a planned randomized study was terminated prematurely after the six patients who had intrathecal methylprednisolone had increased pain and four of the six patients had the area of allodynia increased.[154] Although this method of management of intractable PHN may have been effective in this single study, its association with adhesive arachnoiditis has and should limit its application.

In a systematic review interventional treatments of PHN including transcutaneous electrical nerve stimulation (TENS), botulinum toxin A local injection, cobalamin injection, triamcinolone injection, stellate ganglion block, DRG destruction, pulsed radiofrequency ablation, and intrathecal methylprednisolone and midazolam injection were evaluated. All interventions to treat PHN except for intrathecal methylprednisolone injection was deemed level 2 evidence, substantiating a grade B recommendations. Subcutaneous injections of botulinum toxin A, subcutaneous injections of triamcinolone, TENS, stellate ganglion block, and peripheral nerve stimulation were recommended as treatments to try first given the invasiveness, price, and safety of these techniques. If pain persists, these authors recommended paravertebral blocks or pulsed radiofrequency therapy. With patients in refractory pain, SCS was recommended for consideration while DRG destruction and intrathecal methylprednisolone was reserved for select scenarios requiring comprehensive discussion given the risks associated.[155]

Neuromodulation

With the increase in evidence with concurrent development of neuromodulation technologies, neuromodulation has expanded its role in pain management to addressing PHN as well. The 2014 NACC guidelines reviewed the literature for PHN management with dorsal column SCS and peripheral nerve stimulation (PNS).[156] Since then, several retrospective studies evaluating the role of neuromodulation were performed. In one retrospective study evaluating short term (7–14 days) dorsal column SCS in 46 patients with acute HZ that failed conventional therapies, 69.6% of patients achieved minimally clinically important difference, with 39.1% reporting complete pain relief. The study was limited as no comparative group was available.[157] Another retrospective study of 99 patients with various stages of HZ (acute, subacute) along with PHN who received short term dorsal column SCS treatment were evaluated at one, three, five, and 12 months follow up. The study showed that 97.5% of acute HZ and 84% of subacute HZ patients had pain expressed as VAS scores of two or less at 12 months than 37.5% in patients with PHN. Although no control group was available for comparison, the authors implied that short term dorsal column SCS might decrease the incidence of PHN after an HZ infection.[158]

PNS is another potential modality for the management of PHN. Though most of the literature on this technique are case reports or nestled within a larger neuromodulation cohort, several reviews of this technique discuss the applicability of this procedure in treating PHN. In a case report of two patients with a ten month and 2.5 year follow up, PNS provided an average pain relief of 90%. A review of various neurosurgical techniques for the management of PHN included a review of three PNS studies encompassing ten patients. The procedure was performed after six months of HZ onset with a successful trial before PNS implant. Patients were evaluated at followed up with a mean follow up time of >20 months after IPG implant, where 80% of patients reported satisfactory reduction (>50%) of their pre-procedural pain.[159] Further well controlled trials are needed to validate PNS in the treatment of PHN. However, it may be a promising technique to help patients in the future.

Diabetic Neuropathy

Epidemiology and Risk Factors

The definition of diabetic neuropathy as proposed by the San Antonio Consensus Statement is "demonstrable disorder, either clinically evident or subclinical in the setting of diabetes without other causes of peripheral neuropathy."[160] The diabetic neuropathies are collectively considered a diverse, complex disease that affects many components of the nervous system and exhibits varied clinical manifestations. The condition is a unique neurodegenerative process that preferentially targets sensory axons, autonomic axons, and eventually motor axons to a lesser extent.[161] They can be classified into two main categories: generalized neuropathies versus focal or multifocal neuropathies. Generalized neuropathies include acute sensory neuropathy, chronic sensorimotor distal polyneuropathy, and autonomic neuropathy. Focal and multifocal neuropathies include cranial, truncal, focal limb, and proximal motor neuropathy (amyotrophy), as well as chronic inflammatory demyelinating polyneuropathy.[162]

The prevalence and incidence of DPN have been very difficult to verify given the inconsistencies in clinical diagnostic criteria, variability in patient populations, and wide range of physiologic techniques. The World Health Organization estimated that 150 million people had diabetes in the year 2000, and this number was expected to increase to 366 million by the year 2030.[163] It has been estimated that approximately 56% of patients with DPN will complain of pain that affects their quality of life.[164]

In earlier studies, the prevalence of lower limb pain ranged from 6% to 27%, and DPN affected men and women equally.[165] A study conducted in the United Kingdom involved 356 diabetic patients, most of whom had type two diabetes mellitus (T2DM),

and included a structured questionnaire with a physical examination. Chronic sensorineural DPN (CSDPN) was diagnosed in almost half the patients, but only a third of them complained of pain that had been present for at least one year. The prevalence rate for DPN in this study was 16% compared to 5% for chronic neuropathic pain in a similar population without diabetes. It is also important to note that in this study, 12.5% of patients with DPN did not report symptoms to their physicians, and the 39% who reported pain did not obtain treatment of their pain, which suggests that DPN is undertreated.[166]

A cross-sectional descriptive study reported the prevalence of DPN in patients with diabetes mellitus type two to be 26%. The prevalence of diabetic patients suffering from CSDPN was found to be 44%.[167] A 2009 multicenter study conducted in Belgium included 1111 diabetic patients, types 1 and 2, and estimated the prevalence of CSDPN and DPN.[168] The study was performed with the NeuroPEN device, which tests for pain and monofilament perception and, based on studies, is able to identify CSDPN with confidence.[169] The duration of diabetes in this population was greater in patients with type one than in those with type two, 16 versus 11 years, respectively. The study concluded that the prevalence of CSDPN was 43% and was higher with type two (51%) than with type one (26%) diabetes. The prevalence of lower limb neuropathic pain was 14%, again higher with type two (18%) than with type one (6%).[168]

The prevalence of peripheral neuropathy in type one diabetic patients was quoted as 34% in the Pittsburgh Epidemiology of Diabetes Complications Study, while the SEARCH for Diabetes in Youth Study quoted the prevalence of DPN in youths (average age 15.7) with type one diabetes mellitus (T1DM) as 8.2%.[170,171] In the SEARCH study, the prevalence of DPN was quoted as 26% while the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that 42% of adults with type two diabetes had peripheral neuropathy.[171,172]

The prevalence of diabetic neuropathy increases with increased T2DM duration as the prevalence increased from 8% to 42% when T2DM were monitored over ten years in a 1995 Finnish study.[173] Similar findings were seen in the 2013 Bypass Angioplasty Revascularization Investigation Two Diabetes trial where patients with advanced T2DM in the cohort with 50% confirmed diabetic neuropathy at baseline had a four year cumulative incidence of diabetic neuropathy of 66%–72% in patients who had no neuropathy at baseline.[174] According to these and other studies, the incidence of diabetic neuropathy in patients with T2DM is approximately 6,100 per 100,000 person-years, while it is 2,800 per 100,000 person-years in those with T1DM. The prevalence of diabetic neuropathy in patients with T2DM may be 8%–51%, while the prevalence in patients with T1DM may be 11%–50%.[161]

Risk factors for DPN have been widely studied to prevent its development. The most commonly reported risk factors are age, duration of diabetes, and hemoglobin A_{1C} levels.[161,175] Other risk factors associated with DPN are arterial hypertension,[165] impaired glucose tolerance (IGT),[176] smoking history, alcohol abuse history, and increased height.[177] In a study examining patients with neuropathy of unknown origin, 36% of patients had IGT, 77% of whom had painful neuropathy.[178] Other risk factors shown to have a relationship with the presence of DPN are obesity with low high-density lipoprotein cholesterol and high plasma triglyceride levels.[168] Genetic factors are also considered risk factors based on a study by Galer and colleagues;[164] 56% of patients with DPN also had first- or second-degree relatives suffering from DPN. Specific genes have also been implicated with this condition, including the *ACE* and *MTHFR* polymorphisms.[161]

Pathophysiology

Diabetic neuropathy is theorized to occur by three mechanisms: the polyol pathway, microvascular damage, and glycosylation end-product theories. These three models most likely act simultaneously, but there may also be some overlap between them.[179] Neurotrophic factors, neuronal membrane ion channel dysfunction, mitochondrial dysfunction, and lipid toxicity may likewise play a role in DPN.[180]

The polyol pathway theory proposes that increased blood glucose leads to elevated glucose concentrations within nerve endings. Through a series of reactions, the glucose is converted into sorbitol via the polyol pathway involving aldose reductase and elevation of the fructose level. The high sorbitol and fructose levels subsequently lead to a decrease in sodium-potassium adenosine triphosphatase (Na+, K+-ATPase) activity. Activation of the aldose reductase-depleting cofactor NADPH (reduced nicotinamide adenine dinucleotide phosphate) leads to decreased nitric oxide and glutathione, which inhibits the buffer against oxidative injury and vasodilation and results in chronic ischemia.[179]

In the microvascular damage theory, thickening of the capillary basement membrane along with endothelial cell hyperplasia leads to neuronal ischemia and infarction.[179] The glycosylation end-product theory proposes that interference in axonal transport results in decreased nerve conduction velocity because of chronic hyperglycemia, which results in the deposition of advanced glycosylation end products around peripheral nerves. These end products may also produce NADPH (which activates NADPH oxidase) and contribute to the formation of hydrogen peroxide and increased oxidative stress. These reactive species may have an increased effect in the face of mitochondrial dysfunction resulting in further nerve injury.[180]

Regardless of the mechanism, diabetic neuropathy ultimately develops when the peripheral terminal sensory axons are retracted with the preservation of perikarya (cell bodies). Ultimately the entire neuron, including the perikarya, is affected by diabetes. Schwann cells are targeted by chronic hyperglycemia resulting in damage furthering axonal dysfunction.[161] This progressive axonal damage results in loss of mRNA expressing needed for neurofilament production, promoting oxidative damage and loss of peripheral nerve function.[161]

Nerve growth factors are important in the repair of nerve structure and function after an injury. Low levels of these neurotrophic factors correlate with diabetic neuropathy in animal models. Other factors associated with diabetic neuropathy are abnormal calcium channel activity contributing to cellular injury and death and sodium channel dysfunction playing a role in the genesis of painful neuropathy.[181]

Clinical Features

Acute sensorimotor neuropathy often occurs in association with periods of poor metabolic control, such as uncontrolled glycemic levels or the development of ketoacidosis. This form of neuropathy is very rare.[162] The most common form of peripheral neuropathy is CSDPN, as seen in over 80% of patients with DPN. Patients with CSDPN typically complain of distal, symmetric burning pain that usually involves the feet initially and gradually moves upward in a symmetric fashion. This is because of damage to longer nerves, a

phenomenon known as length-dependent diabetic polyneuropathy.[182]

DPN causes neuropathic pain because of the involvement of small nerve fibers,[183] and diagnosis is achieved through a diligent history and physical examination. One study showed that clinical neurologic examination, including questionnaires, was 23% sensitive and 93% specific in diagnosing DPN.[184] A 2007 study concluded that the development of the DN4 questionnaire has improved diagnostic performance, with a sensitivity of 83% and specificity of 90% in patients with a neuropathic pain score greater than four out of 10.[185] However, such assessment tools, including the Michigan Neuropathy Screening Instrument, the Toronto Clinical Neuropathy Score, and the United Kingdom Screening test, are subjective and rely on examiner familiarity to interpret the results.[186] The initial symptoms in up to 50% of patients with DPN are highly nociceptive and include burning pain, electric or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain, which are typically worse at night. Upper extremity involvement is rare.[187]

Physical examination of the lower limbs typically shows sensory loss of vibration, pressure, pain, temperature perception, and absent ankle reflexes. Loss of touch and pin sensation typically occurs before a loss of proprioception and vibration and is caused by the involvement of large-diameter fibers.[182] This is evaluated with 10 gauge monofilament and tuning fork tests.[169] Gait ataxia may occur with severe neuropathy. In addition, signs of peripheral autonomic dysfunction can be observed, including a warm or cold foot, distended dorsal foot veins, dry skin, and calluses under pressure-bearing areas.[162]

It is important to note that the diagnosis of DPN is a diagnosis of exclusion and that multiple pathologies may mimic this form of neuropathy. The gold standard for diagnosing DPN is with nerve conduction studies that may aid in verifying small and/or large fiber disease and ruling out other mimicking conditions.[186] The differential diagnosis should include peripheral vascular disease, restless legs syndrome, Morton's neuroma, vitamin B12 deficiency, hypothyroidism, and uremia.[162,182]

Several devices may be helpful in diagnosing DPN. DPN-Check, a handheld point of care device that performs a sural nerve conduction test that may serve as a proxy for a full nerve conduction test. It has a reported 95% sensitivity and 71% specificity compared against a reference standard nerve conduction test.[188,189] Neuropad is a device that measures plantar foot sweat production with relatively high sensitivity for detection of small fiber neuropathy. Compared to other tests for detecting DPN, it has a higher sensitivity than the 10 g monofilament test or the biothesiometer test.[190] Sudoscan is a device that quantifies electrochemical reaction between electrodes and chloride ions when sweat glands are stimulated with a sensitivity of 87.5% and specificity of 76.2% in classifying DPN.[191] Although primarily in the validation stage, these instruments may potentially allow for bedside use for confirming the diagnosis of DPN.

Autonomic neuropathy is a common pathology that may occur in patients with chronic diabetes types 1 and 2. This form of neuropathy may be present at any stage of the disease, but it most often affects patients who have had the disease for over 20 years.[192] The parasympathetic, sympathetic, and enteric nerves are affected, and myelinated and unmyelinated nerves are affected and damaged. The condition is considered irreversible, but cardiac sympathetic dysinnervation has been shown to revert with tight glucose control.[193] It affects multiple organ systems, including the cardiovascular, genitourinary, sudomotor, gastrointestinal, and endocrine systems. Some clinical manifestations include resting tachycardia, orthostatic hypotension, distal anhidrosis, bladder dysfunction, erectile dysfunction, female sexual dysfunction, severe constipation, diarrhea, and dysmotility syndrome.[194] In addition, because of the loss of sympathetic tone, vasodilation occurs and leads to the pooling of blood in the lower extremities. This has been proposed to cause osteopenia and is related to the development of Charcot's neuroarthropathy.[195]

Multifocal neuropathies comprise a wide spectrum of neuropathies, including diabetic amyotrophy, truncal neuropathies, cranial neuropathies, and mononeuropathies. Diabetic amyotrophy most often occurs in type two diabetics and is characterized by subacute pain and asymmetrical weakness and atrophy of the proximal lower limb muscles. There may also be involvement of the upper limb muscles and distal end of the lower extremity, but this is rare.[196] Mononeuropathies most commonly involve the ulnar, median, and common peroneal nerves secondary to nerve ischemia because these nerves are more susceptible to injury from compression. Cranial nerve involvement may be present but is extremely rare.[196]

Treatment Options

Treatment of DPN has been widely studied and includes the use of TCAs and SSNRIs, anti-convulsants, opioids, and other modalities. Treatment options can be viewed as approaches to prevent the development of DPN or alleviate its symptoms. As is true for all chronic pain syndromes, a multimodal approach is the most effective therapy for DPN, with the primary aim often focusing on protecting the lower limbs from damage caused by sensory loss or on relieving pain to enhance the quality of life and functionality of each patient.

Lifestyle Modification

Hyperglycemia and insulin deficiency are associated with the pathogenesis of DPN. It appears that glycemic control is one of the most effective treatments to slow the progression of the disease and delay its onset.[1] In a study conducted by the Diabetes Control and Complications Trial Research Group, a total of 1441 patients with insulin-dependent diabetes mellitus (726 of whom had no retinopathy and 715 had mild retinopathy) were monitored for 6.5 years after random assignment to intensive external insulin pump therapy or three or more daily insulin injections. The study concluded that in the group without retinopathy, intensive therapy reduced the risk for development of DPN by 76% compared to conventional therapy. In the retinopathy group, intensive therapy decreased progression by 54%. The study also showed that the progression of microalbuminuria in both groups was reduced by 39%, albuminuria by 54%, and clinical neuropathy by 60% with intensive insulin therapy.[197] Thus tight glycemic control contributes to a delayed onset and slowed progression of DPN.

Recent focus has also emphasized the role of dyslipidemia in the development of DPN. Obesity has been associated as a comorbid risk factor for the development of DPN, and having elevated lipids and triglycerides may contribute to the nerve injury seen in DPN. Non-esterified fatty acids from elevated triglycerides undergo β-oxidation in the cytosol of all peripheral nervous system cells. The byproduct of this process is acetyl Co-A, which is converted into acylcarnitine when accumulated, leading to worsening nerve injury.[198] Reactive oxygen species are also byproducts of β-oxidation, which may stress the endoplasmic reticulum, produce mitochondrial dysfunction, impair axonal transport, and

decrease available ATP.[199] Although dyslipidemia may be associated with the development of DPN, initiation of statins for dyslipidemia has had mixed results. In many mouse models, statins were able to reduce neuropathic pain from oxidative, physical, and chemotherapeutic induced neuropathies.[200,201]

Interestingly, statins were once thought of as a medication class capable of causing neuropathy. A small study in 2002 has implicated statins in causing peripheral neuropathy. However, reanalysis of this study by the same investigators found no association between the two.[202] Further well-controlled studies in humans are needed to establish statins as a preventative means of managing DPN. Regardless, exercise has benefits for lipid and glucose control that may have a role in preventing DPN.[161,203]

Anti-convulsants

Gabapentin has been used as first line therapy for neuropathic pain and has been shown to provide mild relief of pain in patients with DPN. In a randomized, double blind, placebo controlled, eight week trial comparing gabapentin and placebo, it was concluded that daily pain in the gabapentin-treated patients decreased from 6.4 to 3.9 versus a decrease in the placebo group from 6.5 to 5.1. Patients in the gabapentin treatment group also had improved sleep.[204] Another trial comparing the efficacy of gabapentin for DPN used three different forms of recording pain, including the VAS, present pain intensity, and McGill pain questionnaire (MPQ) completed before and after therapy. Only the MPQ showed statistical improvement in pain with gabapentin treatment versus placebo.[205] A 2019 prospective double blind randomized controlled study evaluated the effectiveness of duloxetine and gabapentin in treating DPN over eight weeks. The study found that both medications were effective in lowering VAS scores (64–39 for gabapentin and 62–36 for duloxetine) and improved sleep in both groups. Furthermore, gabapentin was found to be more effective earlier in treatment, while duloxetine had better medication compliance because of fewer side effects.[206]

A clinical synopsis of updated findings from the Cochrane review found that patients on gabapentin with DPN had a higher substantial benefit (38% vs. 21%) and moderate benefit (52% vs. 37%) than placebo.[207] Gabapentin has an NNT of three for overall neuropathic pain. The use of gabapentin for DPN had no effect on the quality of life, but it did yield improvements in sleep and mental health.[205] A systematic review of the literature on the treatment of DPN from 1960 to 2008 recommended that pregabalin be used if medically appropriate before gabapentin. Gabapentin and valproic acid should be considered as alternative therapies for DPN.[208]

A randomized controlled trial comparing pregabalin with placebo in patients with DPN for one to five years showed that 46% of the patients taking a dosage of 300 mg/day, 48% taking 600 mg/day, and 18% taking placebo had greater than a 50% reduction in pain.[209] In a 12 week randomized, double blind, multicenter, placebo controlled trial using a fixed dose of 100 mg/day for one week and 600 mg/day for 11 weeks in one group and flexible doses of 150, 300, 450, and 600 mg/day in the other group concluded that both treatments were superior in reducing neuropathic pain than the group receiving placebo.[210] A 2019 Cochrane review evaluated the efficacy of pregabalin in treating neuropathic pain across 22 studies found the number needed to benefit (NNTB) for 300 mg of pregabalin was 14 while the NNTB for 600 mg pregabalin was 6.1. Meanwhile, the patient global impression of change NNTB was 4.9 for 300 mg pregabalin and 3.7 for 600 mg pregabalin.[211] Thus pregabalin has been shown to be effective in providing relief of neuropathic pain in patients with DPN.

Anti-depressants

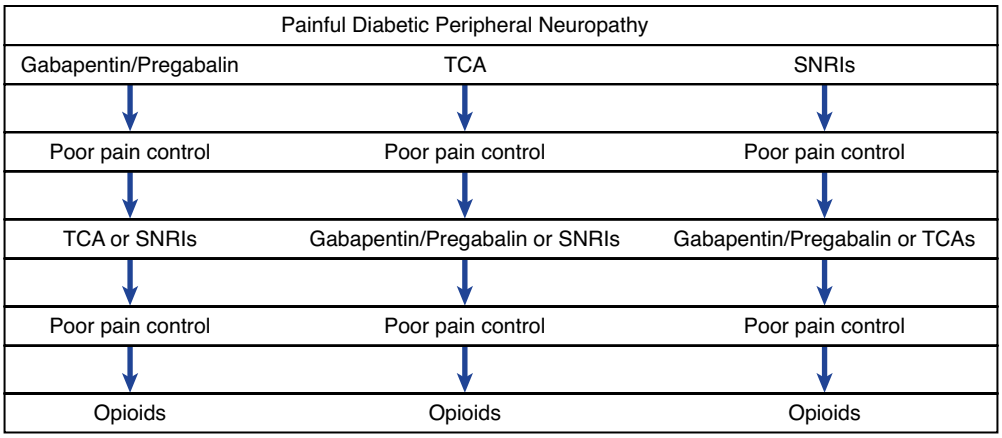
Multiple anti-depressant medications, including TCAs and SSNRIs, have been used for general neuropathic pain with positive results. In one study in which nortriptyline and fluphenazine were given in combination and compared with placebo, the group receiving combination therapy had 63% more patients with greater than a 50% reduction in VAS scores for pain.[212] The NNT for TCAs in patients with DPN was 1.3, as recorded by five randomized trials that established its effectiveness in treating neuropathic pain in those with DPN.[67] In addition, combination therapy with gabapentin has increased the effectiveness of treating PHN and DPN pain.[68] In a multicenter, double blind, randomized, placebo controlled study in which patients were treated with venlafaxine, those patients taking low dose venlafaxine (75 mg) had a 32% reduction from their baseline VAS scores after six weeks, and those taking high dose venlafaxine (150–225 mg) had 50% reduction after six weeks with an NNT of 4.5.[213]

Duloxetine is another SSNRI that has shown promise in relieving neuropathic pain from DPN. Multiple studies have demonstrated duloxetine to be more effective than placebo.[214,206,215] In a randomized, double blind, crossover clinical trial comparing duloxetine with amitriptyline after a six-week treatment concluded that both were effective in treating DPN. The duloxetine group had a 59% reduction in VAS scores with good pain relief, a 21% reduction with moderate pain relief, and a 9% reduction with mild pain relief. Duloxetine was also better tolerated than amitriptyline.[216] When utilizing TCA's and gabapentinoids for management of DPN, care should be taken when prescribing to geriatric populations as both medication classes were associated with increased risk of fall but not necessarily fracture risk.[217]

Opioids and Tramadol

Many studies have shown that opioid medications decrease pain in patients with DPN. The fear of dependency on and addiction to these drugs warrants close observation; opioid medication should be administered only if the patient's condition is unresponsive to non-opioid therapy (Fig. 34.1). Of these agents, tramadol, morphine sulfate, and oxycodone consistently decrease pain from DPN. An open, randomized comparative study of gabapentin versus tramadol and acetaminophen showed that the combination of tramadol and acetaminophen was just as effective in relieving DPN pain as gabapentin.[218] In a randomized, double blind, placebo controlled crossover study using tramadol, the group receiving tramadol experienced relief from polyneuropathy symptoms such as pain, allodynia, and paresthesia (NNT 4.3).[219] However, a 2017 Cochrane review of six randomized controlled trials of tramadol use in neuropathic pain including DPN, PHN, and CIPN showed substantial bias in the studies reviewed, implying the data behind the medication was not a reliable indication of its likely effect.[220]

Oxycodone has also been shown to be effective in treating neuropathic pain in patients with DPN. In a multicenter, randomized, double blind, placebo controlled study comparing controlled-release oxycodone with placebo, it was concluded that pain scores in the groups receiving oxycodone and placebo were 4.1 and 5.3, respectively.[221] This suggests that oxycodone is mildly effective in relieving neuropathic pain in patients with DPN. Another study that added oxycodone to the regimen of diabetic patients already taking gabapentin for neuropathic pain concluded that the use of the combination of these drugs relieved pain more than when gabapentin was used alone.[222] A 2016 Cochrane review of



• **Figure 34.1** Treatment algorithm for painful diabetic peripheral neuropathy. *SNRI*, Serotonin-norepinephrine reuptake inhibitor; *TCA*, tricyclic anti-depressant.

oxycodone use for neuropathic pain showed low quality evidence that oxycodone may have value in treating PHN and DPN but no other neuropathic pain conditions.[223] There are limited data on the use of morphine monotherapy in diabetic patients with neuropathy. A crossover study investigating morphine and gabapentin used as either monotherapy or combination therapy showed that the addition of morphine to gabapentin was more effective with lower doses of each medication.[146] Furthermore, Cochrane reviews of morphine and hydromorphone utilization for treatment of chronic neuropathic pain, including DPN, showed there was insufficient evidence for the use of either medication for chronic neuropathic pain.[224,225]

NMDA Receptor Antagonists

The NMDA receptor plays an important role in processing nociceptive and chronic pain. Thus antagonizing its actions may reduce neuropathic pain. One of the most common NMDA receptor antagonists is dextromethorphan. This drug has been examined in past studies, and it was shown to be efficacious in providing relief of pain in diabetic patients suffering from neuropathy. One study demonstrated that the pain in DPN patients had been reduced by 33% and that 68% of patients receiving dextromethorphan had more than moderate pain relief.[226] A study comparing dextromethorphan with placebo showed a 27% reduction in neuropathic pain in diabetic patients, with higher efficacy achieved with increased doses.[227] Also, it is worth noting that both these studies showed the efficacy of dextromethorphan for DPN but not for PHN.

Despite certain studies demonstrating the efficacy of dextromethorphan in addressing DPN, other studies reported varying results because of the variability of response to a wide range of doses. Furthermore, because of the amount of metabolism that it undergoes, it was argued that it would not have sufficient bioavailability to treat DPN as a monotherapy agent.[228] However, other formulations of dextromethorphan exist in conjunction with subtherapeutic (for cardiac use) dosing of quinidine to inhibit CYP 2D6 activity allows for dextromethorphan to be used as a single agent. A 13-week phase three randomized controlled trial evaluating the efficacy of dextromethorphan-quinidine (45 mg/30 mg or 30 mg/30 mg) in the treatment of DPN was successful at reducing patient reported pain and pain intensity while increasing sleep quality and activity.[228]

Topicals

Topical anesthetics have been deemed safe to use because of their lack of drug interactions, decreased side effects, and lack of titration required. Capsaicin cream (0.075%) has been shown to decrease neuropathic pain with an NNT of 6.6.[229] In addition, 5% lidocaine-medicated plaster has been demonstrated to be as effective as capsaicin, amitriptyline, gabapentin, and pregabalin, as shown in a systemic review study comparing the efficacy of each of these drugs in patients with DPN.[230]

Complementary and Alternative Medicine

Because oxidative stress may play an important role in the pathogenic mechanisms of diabetic neuropathy, the use of antioxidants such as α-lipoic acid may have some beneficial effect in the treatment of diabetic neuropathy. A meta-analysis showed that treatment with α-lipoic acid, 600 mg intravenously for a three-week course, provided effective relief of neuropathic pain and improved neuropathic deficits.[231] A more current study reported significant improvement in neuropathic pain with a 600 mg daily intravenous dose for five weeks (NTT 2.7).[232] Other treatment forms have been suggested for DPN based on its pathophysiology, such as glycation inhibitors, aldose reductase inhibitors, and growth factors, but further research in these areas is necessary.[233]

Acupuncture has been trialed for the management of DPN. In a randomized controlled trial involving 45 patients with DPN, where patients were assigned to either real or sham acupuncture, a 15 point drop in VAS was observed in patients receiving acupuncture.[234] A 2017 meta-analysis of four randomized controlled trials where acupuncture or electroacupuncture was used to treat patients with DPN showed that either form of acupuncture was successful in treating DPN. However, the majority of the studies had methodologic problems, and further well-controlled trials were needed.[235]

Neuromodulation

Growing interest has developed in utilizing neuromodulation for the treatment of DPN. Several studies in mice have shown that SCS may alleviate or attenuate mechanical hypersensitivity in DPN models utilizing various wave forms.[236–238] A case series have been published implicating a possible role for certain waveforms in the successful management of DPN.[239] Traditional targets of dorsal column and DRG neuromodulation are being investigated.

A study investigating the role of high-frequency dorsal column SCS in the management of painful DPN has recently been published on a cohort of 216 randomized patients in the SENZA-PDN study for a 6 month period.[240] Patients with greater than a 1 year history of PDN refractory to 2 analgesics including a gabapentinoid with a VAS for lower extremity pain of 5 or more, a BMI of 45 or less, oral morphine equivalents less than 120 mg a day, and a hemoglobbin A1c of 10 or less were eligible for enrollment in the study. These patients were trialed and, if found to have improved pain, implanted with the study device. Results of the study showed that patients treated with SCS had a statistically significant improvement of pain superior to conservative medical management (CMM) with a mean decrease in VAS of 5.9 compared to a mean decrease of 0.1 at 6 months. Further, SCS patients were noted have an improved sensory exam at 6 months compared to patients managed with CMM. Additional studies are needed to evaluate and verify the durable efficacy of this modality and other wave forms in managing DPN.

HIV-Related Pain Syndromes

Epidemiology

It is estimated that there are roughly 37.9 million people living with Human Immunodeficiency Virus (HIV)/acquired immunodeficiency syndrome (AIDS) worldwide as of 2018.[241] With the development and widespread use of highly active antiretroviral therapy (HAART) and the resultant decrease in opportunistic infections of the central nervous system, polyneuropathy has become the most prevalent neurologic complication associated with HIV infection.[242] This disease affects the patient's immune and nervous systems. As the patient progresses through different stages of the disease, a variety of neurologic complications arise that are directly or indirectly related to HIV infection.[243]

Although symptomatic neuropathy occurs in 10%–35% of individuals seropositive for HIV, pathologic abnormalities exist in almost all those with end-stage AIDS.[244] A systematic review in which multiple studies were compiled in the hope of determining the incidence and prevalence of neuropathy in HIV-infected patients found a high level of variation across all the studies. The prevalence of neuropathy ranged from 1.2% to 69.4%. The rate of development of neuropathy per 100 person-years in HIV patients ranged from 0.7 to 39.7, with a greater risk for neuropathy in older patients and those with more advanced disease.[245]

Multiple neurologic deficits occur with HIV infection, but the two most common forms of HIV-related sensory neuropathy (HIV-SN) are distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN). DSP is because of the viral infection itself, whereas ATN is because of medical treatment of the viral disease.[242] The more common of the two disorders is DSP. The most common risk factors for the development of HIV-SN before the introduction of HAART were older age and advanced disease states (such as high plasma viral load and low CD4+ cell count).[246] After initiation of HAART, risk factors for the development of neuropathy became more ambiguous and included older age, CD4+ count lower than 50 cells/mm, nutritional deficit, use of dideoxynucleoside reverse transcriptase inhibitors, and exposure to protease and alcohol.[247] Medications associated with causing ATN include stavudine (d4T), didanosine (ddI), and zalcitabine (ddC), collectively known as dideoxynucleoside reverse transcriptase inhibitors or "D-drugs."[242]

Clinical Features

Although these HIV-SN disorders may represent two distinct entities,[248] the clinical syndrome and pathophysiologic manifestation of the two disorders are almost indistinguishable. In the case of ATN, the time course of the illness and the temporal relationship to commencement of antiretroviral therapy represent the primary differentiating characteristic. The onset of DSP can occur in either the subacute or chronic phase or following the development of an AIDS-defining illness. The clinical manifestations of ATN can appear within the first week to six months after the initiation of antiretroviral therapy and may subside after its cessation.

The clinical features of HIV-SN are dominated by painful dysesthesia, allodynia, and hyperalgesia. Its onset is often gradual, and it most commonly begins with bilateral lower extremity involvement. The neuropathy progresses in a length-dependent fashion with a worsening gradient of disease from distal structures to those more proximal. The dysesthesia commonly involves the soles of the feet first and progresses proximally; when the symptoms encompass the dermatomes of the knee, the patient will frequently report finger involvement. Though patients with DSP may be asymptomatic, most present with neurologic deficits. A 2014 study found that neuropathy was detected in 35% of participates 3.5 months after initial HIV transmission.[249]

The first symptoms noted are often numbness or burning sensations following a diurnal cycle, with the pain being worse at night. Shortly after that, patients will report allodynia (a stimulus previously not found to be noxious is perceived as painful) and hyperalgesia (a lower pain threshold) of the involved structures. Therefore wearing shoes and walking become painful, and the patient's gait becomes antalgic. There is minimal subjective or objective motor involvement, and pain is typically limited to the intrinsic muscles of the foot. Besides the sensory findings, physical examination reveals a diminution or loss of ankle reflexes.[250]

Diagnostic Studies

There is currently no gold standard for the diagnosis of DSP. In addition, the optimal combination of diagnostic studies has yet to be defined. The disease process remains primarily a clinical diagnosis.[251] The neuropathy may be secondary to many other physiologic processes for which blood work must be obtained for exclusion, such as vitamin B12 deficiency, diabetes mellitus, hypothyroidism, IGT, and syphilis.[250] In a nonrandomized, cross-sectional study, HIV patients with axonal peripheral neuropathy who were taking neurotoxic nucleoside analogs had their acetylcarnitine serum levels measured. Patients suffering from neuropathy while taking nucleoside analog medications had a deficiency in acetylcarnitine and were nutritionally deficient.[252] Although the level of acetylcarnitine may be used for the diagnosis of ATN, more studies are necessary.

Nerve conduction studies are not necessary for the diagnosis of DSP and will show an axonal, length-dependent, sensory polyneuropathy. Needle electromyograms are of no significant benefit because the findings are usually normal, but they may show chronic denervation and reinnervation.[253] Punch skin biopsy specimens from the distal end of the calf and proximal part of the thigh may be used to detect small fiber neuropathy by measuring intraepidermal nerve fiber density.[248] The lower the intraepidermal density, the greater the likelihood of DSP symptoms developing

and the greater the neuropathic pain level. Epidermal nerve fiber density may be used as a quantitative marker in clinical trials of neurodegenerative agents and predict the likelihood of symptoms developing in an asymptomatic patient.[254] DRG neuronal loss has been reported, although the reduction is more modest than distal axon loss.[255]

Pathophysiology

DSP and ATN are clinically similar but have distinct pathophysiology. The exact mechanism of the disease process is not fully understood, but it is hypothesized that there are multiple mechanisms at work that eventually cause axonal injury. The peripheral and central nerve toxicity related to HIV infection may be because of cytokine-mediated effects because HIV does not infect axons or Schwann cells. The gp120 protein is an HIV-associated protein thought to play a key role in pathogenesis through the ligation of chemokine receptors located on glial cells and neurons.[256] It may also play a role on chemokine receptors related to Schwann cell-to-neuron interaction.[257] Damage to axons occurs secondary to the inflammatory reaction in the nerve and surrounding tissues, which eventually leads to the characteristic pain seen in DSP. This hypothesis has been supported by animal studies in which gp120 was found to produce pain in rats when administered epineurally into the sciatic nerve[258] and intradermally into the paw.[259] The indirect causes of DSP pain are thought to be mediated by inflammatory injury. They can be divided into peripheral and central mechanisms. The peripheral hypothesis proposes that the pain results from the spontaneous activity of uninjured pain-transmitting or C fibers after injury to adjacent fibers. Inflammatory mediators released by macrophages may further sensitize these fibers. The central hypothesis involves an alteration in ion channels in the DRG combined with changes in the spinal cord dorsal horn that result in "central sensitization."[260]

ATN primarily occurs because of the use of nucleoside reverse transcriptase inhibitors and typically ensues within a year of beginning treatment or in patients with preexisting peripheral neuropathy.[261] The mechanism for ATN is currently unknown, but mitochondrial dysfunction as a result of abnormal mitochondria in Schwann cells and axons has been shown to play a role.[262]

Data have also shown that the depletion of mitochondrial Deoxyribonucleic Acid (DNA) seen in AIDS patients treated with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) leads to increased serum lactate levels and increased cell death.[263] In recent years, some of the protease inhibitor medications, more specifically, indinavir, ritonavir, and saquinavir, have led to an increased risk for mitochondrial toxicity that is partly because of their enhanced ability to penetrate within the neural compartments.[264]

Treatment

No medication is currently approved by the Food and Drug Administration for the treatment of HIV-SN. Most of the therapeutic modalities available have been tested and approved for other neuropathic pain (PHN and DPN). The therapeutic approach for HIV-SN first involves removing or reducing the dosage of the antiretroviral medication whenever possible.[265] Also, the patient's metabolic and nutritional status must be optimized to exclude alternative explanations for the neurologic symptoms (see "Diagnostic Studies") before initiating any other forms of therapy. Greater placebo response was attributed to the difficulty in evaluating analgesic efficacy in treating patients with HIV-SN. However, a systematic meta-analysis comparing placebo responses between HIV-SN and DPN found no statistical difference.[265,266]

Many different medications have been studied for the treatment of this form of neuropathic pain with no great success. Intranasal peptide T did not show any effectiveness in a randomized, double blind multicenter study in which patients with HIV-SN received either placebo or 6 mg/day of peptide T.[267] One medication that has been proved to be effective in relieving pain is recombinant human nerve growth factor, but it does not provide any evidence of neuroregeneration.[268]

Acetyl-L-carnitine (ALCAR) increases neurotrophic support of sensory neurons, as demonstrated in a double blind, parallel-group, placebo controlled, multicenter study. The groups were divided into those receiving placebo and those receiving ALCAR intramuscularly for 14 days, followed by ALCAR orally for 42 days. The group receiving ALCAR had significant improvement in pain.[269] Erythropoietin, a hematopoietic growth factor, was shown to prevent axonal degeneration in cells that had been exposed to HIV gp120 protein, but further studies are needed.[270] Amitriptyline and mexiletine have proved effective in relieving neuropathic pain in patients with DPN and PHN. Unfortunately, they did not prove to be more beneficial for HIV-SN than placebo in a randomized, double blind study.[271] Other medications such as duloxetine and venlafaxine, both SSNRIs, have been approved for the treatment of DPN, but further research is required to demonstrate their efficacy in relieving pain in patients with HIV-SN. Acetaminophen and nonsteroidal anti-inflammatory drugs have limited efficacy in the management of DSP. In cases of severe/refractory cases, opioids may be considered as an additive agent.[250]

Gabapentin has been shown to be effective in treating all types of neuropathy, including HIV-SN pain. In a placebo controlled trial in which patients were treated with gabapentin (1200 to 3600 mg/day) or placebo for four weeks and then an open trial for two weeks, the group receiving gabapentin experienced improvement in pain by 44% and improvement in sleep by 49% when compared with the placebo group, with the most statistically significant side effect being somnolence.[272]

Pregabalin is also very effective in relieving neuropathic pain. A recent randomized, double blind, placebo controlled, 14-week parallel-group trial testing the efficacy of pregabalin showed that there was no benefit in taking pregabalin over placebo.[273] Lamotrigine, 300 mg/day, was found to significantly reduce pain in patients with DSP and ATN in a randomized controlled trial.[274] Topical medication has also been studied for HIV-SN, including 5% lidocaine and high dose capsaicin cream. In a randomized controlled trial, 5% lidocaine cream was shown to be ineffective in treating HIV-SN pain.[275] A double blind, multicenter, randomized trial using high dose capsaicin cream demonstrated pain relief in patients with HIV-SN.[276]

Cannabis may have a role in treating HIV-SN. A randomized placebo controlled trial evaluated the use of cannabis (3.56% tetrahydrocannabinol [THC]) to placebo cigarettes in 50 patients with HIV-SN. Patients using cannabis reported a 34% reduction in daily pain than placebo (17%). A phase II, double blind placebo controlled crossover study of 28 patients with HIV-SN who failed two prior analgesic agents was performed comparing 1%-8% THC use to placebo in the management of their HIV-SN. Forty-six percent of patients who used cannabis reported >30% pain relief than the placebo group (18%). However, the

duration of treatment and primary end point of both studies was only five days.[277,278] Further studies are needed to verify long term outcomes.

Chemotherapy Induced Peripheral Neuropathy

In 2018 the World Health Organization attributed one in six deaths to cancer. The incidence of cancer in 2018 was estimated to be 18.1 million new cases with a cumulative lifetime risk of one in eight for men and one in ten for women.[279] Chemotherapy and surgery are the mainstays for the management of cancer. As cancer treatment algorithms evolve with increased efficacy, the number of cancer survivors are increasing. The five-year survival rate of cancer has increased dramatically since the 1960s from 39% to 70% among white and 27% to 63% among black patients.[280] Chemotherapy induced peripheral neuropathy (CIPN) is a neuropathic pain condition that results from chemotherapy exposure. Many cancer patients develop CIPN that continues long after their disease is in remission, and CIPN is developing into one of the most burdensome long term side effects from cancer.[281]

Epidemiology

Early studies have reported that CIPN occurred in roughly 90% of all patients who received neurotoxic chemotherapy.[282] Subsequent studies have found that CIPN more accurately had a prevalence of 68.1% within the first month of chemotherapy, 60.0% at three months, and 30.0% at six months or more.[283] Overall, it seems that the prevalence was found to be between 36% and 58% in patients actively on cancer treatment and patients 12 years after treatment.[284–286] CIPN presents a unique scenario as dose reductions of chemotherapy may help address the pain and concurrently increase the risk of morbidity and mortality from undertreatment of cancer. With increased survivorship from cancer diagnosis, CIPN has long-lasting consequences as it often continues beyond the period of treatment and once the cancer is in remission. Agents that may cause CIPN include platinum containing compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine and vinblastine), proteasome inhibitors (bortezomib), epothilones (ixabepilone), immune checkpoint inhibitors, antibody drug conjugates, and other chemotherapeutics (eribulin, thalidomide, lenalidomide).[287]

The main risk factors for CIPN include cancer type (because of the chemotherapeutics required to treat specific cancers) and the cumulative dose of the chemotherapeutic agent. Solid tumors (colorectal, breast, gynecologic, testicular, lung) and hematologic cancers are the most common cancers requiring neurotoxic chemotherapy.[287] Other risk factors include baseline neuropathy, age, concurrent chemotherapy treatment, smoking, early cancer diagnosis, and cancer treatment protocols utilizing drugs that can cause CIPN.[287,288]

Genetic markers have been implicated to be associated with CIPN. A Genome Wide Association Study (GWAS) on patients with multiple myeloma found 13 single nucleotide peptide polymorphisms associated with CIPN development.[289] A similar approach was performed in breast cancer patients with CIPN from taxane exposure where the GWAS revealed an association with an allele gene variant that may decrease the risk of developing CIPN when exposed to taxane.[290] However, current efforts have been unsuccessful in identifying genes that serve to reliably predict susceptibility to this condition.[291]

Clinical Features

Similar to DPN, CIPN manifests in a glove and stocking distribution with a proximal spread in more severe cases. Though largely a sensory neuropathy, patients may develop autonomic dysfunction, fine motor dysfunction, and decreased proprioception.[292] Patients can report either negative (impaired touch, pinprick vibration perception, imbalance) or positive (paresthesia, dysesthesia, neuropathic pain) symptoms in a distal to proximal fashion. Unique to exposure to platinum containing compounds, patients may report worsening symptoms months after cessation of chemotherapy, presenting the "coasting" phenomenon.[281]

Aside from pain and sensory loss, CIPN also negatively impacts the functionality and quality of life of afflicted patients. In a comparative cross-sectional descriptive study comparing cancer patients with all cause neuropathic pain to those without neuropathic pain on hospice found that 40% of all patients had neuropathic symptoms, of which 76.7% reported pain.[286] These patients are noted to be at high risk for falls, and the majority have decreased sleep quality.[293] In a prospective study evaluating SPADE symptoms in a cohort of 65 cancer patients with CIPN, 69.5% of patients reported sleep impairment.[294]

Diagnostic Studies

The diagnosis of CIPN is largely a clinical diagnosis. Care to obtain a detailed history and physical focusing on the natural history of other causes for neuropathy, including alcohol use, diabetes, nutritional deficiencies, and other exposures, should be exercised to rule out other causes of peripheral neuropathy. Although no gold standard exists for diagnosing CIPN, clinical tools including MPQ, brief pain inventory, Leeds assessment of neuropathic symptoms and signs, and Douleur neuropathique 4 may be helpful to characterize and trend the patient's pain. Specific tools for assessment of CIPN exist, including the Ajani scale, the functional assessment of cancer therapy-taxane, CIPN20, and the NCI common toxicity criteria, but may not truly reflect the incidence of neuropathy and suffer from inter-observer variations.[288,292]

Pathophysiology

Several theories regard the mechanism by which CIPN develops, as varying classifications of chemotherapeutics have different mechanisms of action and end targets. Overall, these theories fall within three main categories, including mitochondrial dysfunction with oxidative stress, neuroinflammation, and ion channel dysfunction although each associated chemotherapeutic has a target that is most likely affected.[288]

Many chemotherapeutics target nuclear DNA. However, mitochondrial DNA may be affected as well. Unlike nuclear DNA, mitochondrial DNA does not have a robust repair mechanism, and damage may result in mitochondrial dysfunction. Studies in rats exposed to paclitaxel producing painful peripheral neuropathy revealed intact myelin and DRG structure but swollen, atypical mitochondria in myelinated and unmyelinated neurons that correlated with the pain behavior displayed by the rats.[295] Another rat study with cisplatin induced peripheral neuropathy showed that DRG cell cultures from affected rats displayed dysfunctional mitochondrial transport that was reversible over time.[296] Among

the many roles of mitochondria, regulation of reactive oxygen species (ROS) plays a particularly important role, especially in light of chemotherapeutics, which inherently increases the amount of ROS. In a study of breast cancer patients, blood was evaluated in those with and without CIPN (from paclitaxel), which showed mitochondrial dysfunction pathways including those related to oxidative stress in patients with CIPN but not those without.[297]

Neuroinflammation plays a role in the development of chronic pain states. Certain cell types, including glial cells, are activated and play a role in inflammation and injury in chronic pain. In recent studies, the focus has shifted to astrocyte activation from chemotherapeutics as playing a role in maintaining the chronic pain state from CIPN. In rat models with oxaliplatin and bortezomib induced peripheral neuropathy, astrocyte but not microglial activation correlated to chemotherapeutic treatment.[298] These astrocytes contain adenosine kinase, which removes extracellular adenosine, a neuroprotective agent released to counter neuropathologic changes. A study in rodents with overexpression of adenosine kinase resulted in pro-inflammatory IL1ß expression indicating a possible mechanism by which dysfunctional astrocytes may result in CIPN.[299] Chemotherapies have also been associated with increased pro-inflammatory chemokine release, including TNF-α, bradykinin, and nerve growth factors, while downregulating anti-inflammatory chemokines.[300] Further studies are needed to elucidate the cellular mechanisms by which CIPN occurs.

It has been noted that certain chemotherapeutics (namely taxanes, platinum containing compounds, and vinca alkaloids) may modulate primary afferent neuron ion channel expression.[301] Channels reportedly affected include sodium channels, potassium channels, and to some extent, calcium channels. Sodium channel and potassium channel dysfunction have been found in acute oxaliplatin toxicity resulting in cold hypersensitivity by causing delayed sodium channel inactivation and decreased potassium receptor expression, respectively.[302,303] Studies in rats exposed to paclitaxel have shown an increase in calcium channel currents in the DRG by increased channel expression.[304] Despite these findings, targeting specific ion channels has had mixed results.

Treatment

Prevention and Physical Therapy

There is great emphasis on prevention in the management of CIPN, as many neuropathic treatments are ineffective for this condition. A 2014 review of 48 randomized clinical trials by the American Society of Clinical Oncology to provide guidance for the prevention of CIPN revealed that no agent is recommended given the lack of high quality evidence.[305] Similarly, a 2014 Cochrane review for agents to prevent CIPN from platinum containing chemotherapeutics concluded that there was insufficient evidence to recommend chemoprotective agents.[306] As such, a careful balance between chemotherapeutic dose reduction to achieve efficacious cancer treatment while minimizing the risk or severity of CIPN development needs to be weighed by oncologists.

Aside from neuropathic pain and numbness, patients consequently have difficulties with gait, balance, and falls. Although physical therapy has not been successful in reducing pain, work with physical therapists has been effective in addressing functional deficits as a result of CIPN. In a prospective study, 29 cancer survivors with CIPN underwent an eight-week exercise intervention under the guidance of physical therapists. There was a statistically significant improvement in objective and patient reported measures of dynamic balance, standing balance, mobility, and quality of life compared to pre-exercise intervention.[307]

Anti-convulsants

Gabapentin and pregabalin are effective in managing many neuropathic pain conditions. However, their use has not been as effective in managing patients with CIPN. In a study evaluating 61 ovarian cancer patients who developed CIPN, eligible patients were trialed on gabapentin with observed improvement in pain and neurologic deficits, but no improvement in quality of life was observed.[308] Gabapentin was further evaluated in a randomized, double blind placebo controlled crossover controlled trial of 115 patients with CIPN that revealed statistically similarly symptom severity despite the use of gabapentin.[309]

Comparatively, pregabalin may be more effective than gabapentin for symptom improvement. In a study of 120 cancer patients with CIPN, patients were trialed on either amitriptyline, gabapentin, pregabalin, or placebo with oral morphine for breakthrough pain for four weeks.[310] At the end of the trial, there was a statistically significant difference in morphine sparing pain score improvement in the pregabalin group than gabapentin and amitriptyline. One study evaluated the concurrent use of oxycodone/naloxone with either gabapentin or pregabalin in 72 patients with CIPN who had previously had inadequate symptom control alone with gabapentinoids. Over the course of four weeks, patients reported an NRS reduction of 1.29.[311]

Anti-depressants

Of the various classes of anti-depressants, the class of norepinephrine and serotonin reuptake inhibitors have shown the most promise in treating CIPN. In particular, duloxetine has been shown to be most effective in treating CIPN. A multicenter, randomized, double blinded, placebo controlled, crossover study of 231 patients with CIPN evaluated the efficacy of 60 mg daily duloxetine in pain management. The observed mean difference in pain score between duloxetine and placebo was 0.73, with 59% of patients on duloxetine reporting decreased pain than 38% of placebo.[312] Compared to venlafaxine in a randomized controlled trial with placebo, duloxetine was found to significantly reduce neuropathic pain grade by week two than venlafaxine or placebo. Reduction in cranial, motor, and sensory neuropathy was also found to be greater in patients treated with duloxetine than venlafaxine or placebo.[313]

Topicals

Useful adjuncts in treating other forms of neuropathic pain, there may be a role of topical anesthetics in this patient population. Like other neuropathic pain types, lidocaine patches have had anecdotal success, but evidence from studies to support their use is lacking.[314] Topical 1% menthol cream was utilized for the treatment of cancer associated neuropathic pain in a proof of concept study where 51 patients (35/51 with CIPN) were followed for four to six weeks. At the study conclusion, 82% of all patients reported an improvement in their Brief Pain Inventory (BPI) score, mood, catastrophizing, walking ability, and sensation.[315] Capsaicin (8%) has also been reported to provide pain relief and sensory improvement in patients with CIPN.[316] Other studies utilizing multi-component creams including baclofen, amitriptyline, and ketamine in pluronic lecithin organogel (BAK-PLO) were tried on patients with CIPN in a double blinded placebo controlled trial over four

weeks. Patients utilizing BAK-PLO experienced greater sensory and motor improvement than placebo.[317] However, further larger studies are needed to fully evaluate traditional and nontraditional topical analgesics for CIPN treatment.

Cannabinoids

Cannabinoids have been found to provide beneficial treatment for several other neuropathic pain conditions, but their use may be limited by the effects on the CNS.[318] Activation of the cannabinoid receptors (CB1 and CB2) have been found to have beneficial effects on CIPN in animals studies. A peripherally acting CB1 agonist (PrNMI) was found to successfully suppress allodynic effects in cisplatin induced CIPN rat models.[319] In a study in rats, a CB2 agonist was successful in suppressing mechanical and cold allodynia in cisplatin and paclitaxel induced CIPN models.[320] Further animal studies have shown that CB2 specific agonist MDA7 attenuated the behavior and molecular changes in rats associated with microglial dysregulation and CIPN. Despite these successes in animal models, large well-controlled studies are needed to verify use in humans for the management of CIPN.

Neuromodulation

Much of the literature on CIPN treatment with neuromodulation is limited to case reports of DRG or dorsal column stimulation.[321,322] There may be a role for neuromodulation in the treatment of CIPN, but randomized controlled trials are needed to fully assess their efficacy and role in this disease.

Summary

Despite the diversity of conditions and pathophysiology characterized by neuropathic pain, many of the underlying treatment options are comparable but not identical. Traditional systemic analgesic agents, such as anti-depressants, anti-convulsants, local anesthetics, and opioids, are typically the mainstay of treatment of neuropathic pain, although the efficacy of individual classes of agents varies with the specific type of neuropathic pain. Few high quality trials are available as interventional options for the treatment of neuropathic pain. Clinicians should be aware of the paucity and support the use of traditional interventional options in some cases.

Key Points

- The most commonly used clinical diagnostic criteria for CRPS types one and two have low specificity and high sensitivity, leading to overdiagnosis of this pain syndrome.
- In 2007, research criteria (also known as the Budapest criteria) were published that included objective signs of pathology characteristic of patients with CRPS[6] (see Box 34.2).
- Psychological factors such as depression, personality disorders, and anxiety have no correlation with CRPS patients, suggesting no specific type of CRPS personality.
- A double blind, randomized, placebo controlled, parallel-group trial studying the effects of subanesthetic intravenous dosing for four days in patients with CRPS showed decreased levels of pain but a progressive increase in pain from the first week after infusion to the 12th week. Minor and rare side effects such as nausea, vomiting, and psychomimetic effects developed in patients treated with ketamine infusion.
- In a randomized trial, patients with CRPS were separated into two groups: SCS with physical therapy and physical therapy only. This study showed that SCS provided significant improvement in pain for the first two years.
- The acute phase of herpes zoster is characterized by a maculopapular vesicular rash that crusts over after one to two weeks and leads to a burning sensation, hyperesthesia, itching, and severe pain. Prodromal symptoms that may occur one to five days before the rash include headache, fever, malaise, abnormal skin sensation, and photophobia. PHN may occur two weeks after the presence of herpes zoster and is the chronic form of the disease.
- Medications such as gabapentin, pregabalin, tramadol, and topical lidocaine are considered first line treatments because they have been shown to be most well tolerated by the (commonly elderly) patient population. Other medications shown to help in relieving the pain associated with PHN are tricyclic and serotonin-norepinephrine reuptake inhibitor anti-depressants, opioids, and topical capsaicin cream (see Table 34.2).
- The initial symptoms in up to 50% of patients with painful DPN are highly nociceptive and include burning pain, electric or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain, which are typically worse at night. Upper extremity involvement is rare.[187]
- The rate of development of neuropathy per 100 person-years in patients infected with HIV ranged from 0.7 to 39.7, with a greater risk for neuropathy in older patients and those with more advanced disease.[245]
- Lamotrigine, gabapentin, and topical capsaicin are effective in the treatment of HIV-associated neuropathic pain, but amitriptyline, topical lidocaine, and pregabalin are ineffective.
- The current evidence for the management of CIPN is lacking. Emphasis should be placed on prevention by balancing the duration and dose of the chemotherapeutic. In situations where a patient has developed CIPN, pregabalin and duloxetine have shown the most promise for managing neuropathic symptoms.

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35

Evaluation and Treatment of Complex Regional Pain Syndrome

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Introduction

As defined by the International Association for the Study of Pain (IASP), complex regional pain syndrome (CRPS) is a collection of locally painful conditions following trauma, usually manifesting distally and exceeding the clinical course of the original trauma in severity and duration, often resulting in a significant impairment of motor skills, and is characterized by a variable progression over time. CRPS can develop as a complication after surgery or trauma. The spontaneous occurrence has been described, but the question is whether there was no unnoticed trauma in these cases.[1] In the literature, the syndrome has been given more than 72 different names, including well-known names such as Sudeck dystrophy, posttraumatic dystrophy, and sympathetic reflex dystrophy.

At a meeting of the IASP in Orlando in 1992, it was agreed that only the term "complex regional pain syndrome" would henceforth be used. A distinction has been made between type 1 without and type 2 with demonstrable nerve damage.[2] Over time, it was proposed to add a third type, namely CRPS not otherwise specified, for conditions that meet the diagnostic criteria only to a limited extent but where no other diagnosis can be made. In clinical practice, "warm" CRPS (in which the skin is red, strongly perfused, and warm) is distinguished from "cold" CRPS (in which the skin is bluish, poorly perfused, and cold).[3]

CRPS has long been seen as a curious disease in which perception and behavior played a major role, which was self-limiting and did not last too long. Recent research has pointed out the opposite. CRPS is a complex condition based on an interaction between the immune system and the nervous system that severely damages various tissues and leads to severe limitations and ultimately disability. Genetic and immunologic factors can also play a role; the unraveling of pathophysiology has only just begun. The disease has serious consequences for functionality and quality of life and leads to high direct and indirect health costs.

This chapter will discuss the pathophysiology, epidemiology, clinical features, and treatment of CRPS. A review of the pharmacologic management will be brief since there is an expanded discussion of the topic in Chapter 34. Neuromodulatory treatments are also successful, as there is a detailed discussion of spinal cord stimulation, stimulation of the dorsal root ganglion (DRG), and peripheral nerve stimulation in Chapter 71.

Pathophysiology

During the last two decades, important discoveries have resulted in a better understanding of the pathophysiology.[4] Several mechanisms seem to play a role next to each other. A distinction can be made between afferent mechanisms, such as inflammation and endothelial dysfunction, efferent mechanisms, such as changes in the somatosensory and autonomic nervous system, and central mechanisms, including cortical reorganization and psychological factors.

Afferent Mechanisms

Some of the symptoms of CRPS are similar to those of inflammation, such as pain, redness, warmth, and swelling. Sudeck suggested more than 100 years ago that CRPS could be a form of bone inflammation, but this idea could not be confirmed because CRPS is not associated with fever, increased blood sedimentation rate, increased C-reactive protein (CRP), and leukocytosis.

However, over the past 20 years, several studies have shown that inflammation is an important mechanism in the development and maintenance of CRPS.[5] Increased levels of two neuropeptides, C-gene related peptide and substance-P, have been demonstrated in the serum of CRPS patients.

Levels of the pro-inflammatory cytokines, interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α, measured in artificial blisters on the skin of CRPS patients, were found to be elevated in the affected extremity.[6] TNF-α and IL-6 levels in skin biopsies from fracture patients with and without CRPS were higher in patients with CRPS.[7] Serum levels of soluble TNF receptors, and the pro-inflammatory cytokines TNF-α, IL-1, and IL-8 are increased in patients with early CRPS. In contrast, the levels of anti-inflammatory cytokines such as IL- 4, IL-10, and transforming growth factor β-1 are reduced.[8]

Artificial blisters on the skin of CRPS patients have also been found to contain more tryptase in the affected extremity. Tryptase is a marker of mast cell activity. Therefore it seems likely that mast cells are involved in the release of pro-inflammatory cytokines in CRPS.

The involvement of T lymphocytes in CRPS has recently been demonstrated in a study in which levels of the soluble interleukin two receptor (sIL-2R) were higher in serum from CRPS patients. The level of sIl-2R is a biomarker of inflammatory activity. However,

it is important to realize that it is not a disease-specific biomarker; sIL-2R may also be increased in other syndromes. It is a specific measure of inflammatory activity. Signs and symptoms remain the cornerstone for the diagnosis of CRPS.[9]

In patients with CRPS, signs of hypoxia, such as increased lactate levels, muscle acidosis, and specific histopathologic features, have been found in local tissue. A decrease in the capillary oxygenation of the skin was observed with micro-light-guided spectroscopy.

In other studies, an imbalance between the vasodilating nitric oxide (NO) and the vasoconstricting endothelin-1 (ET-1) has been shown, in artificial blisters on the skin of patients with cold CRPS, the NO level is lower, and the ET-1 level is higher in the affected extremity.[10] This is probably a direct consequence of persistent inflammation.

Skin biopsies showed an increase in α receptors.[11] It was previously believed to be because of an autonomic nervous system disorder. Recent research has also shown a direct influence of persistent inflammation on the increase in α receptors. In the affected extremities of CRPS-1 patients, histopathologic examination of skin biopsies revealed a loss of C and Aδ fibers and abnormal branching nerve endings. In one study, axonal density was found to be 29% lower in CRPS patients.[12] This is probably the result of ongoing inflammation.

According to the IASP definition, CRPS-1 does not show nerve damage in classic neurophysiologic research. The fact that CRPS1 may have an unrecognized small fiber neuropathy makes the distinction between CRPS-1 and CRPS-2 somewhat artificial.[13]

Efferent Mechanisms

Chronic stimulation of nociceptors can lead to central sensitization, pain, and sensory disturbances. Previously, these signs and symptoms have been termed neuropathic. Today, we use the term nociplastic pain, which is a pain that arises from altered nociception despite the absence of clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of a disease or lesion of the somatosensory system causing pain.[14]

The sensory disturbances in CRPS are related not only to the pathology at the affected site but also to disturbances at the spinal or supraspinal level. Changes in the central nervous system, central sensitization, and neuroplasticity can lead to hypersensitivity to normal stimuli (allodynia) and painful stimuli (hyperalgesia). The exact mechanisms have not yet been fully elucidated. The action of neurotransmitters on postsynaptic receptors for N-methyl-D-aspartate, aminomethylphosphonic acid (AMPA), and neurokinin-1 (NK1) are involved. CRPS is also referred to as sympathetic reflex dystrophy because of the signs and symptoms of autonomic dysfunction. In the acute phase of CRPS, both phasic and tonic sympathetic reflexes in the affected extremity are disturbed.[15] Noradrenaline levels in the affected extremity are lower. Changes in the spinal cord or higher centers of the central nervous system are likely to play a role in the dysregulation of the autonomic nervous system. In the past, dysfunction of the sympathetic nervous system has been used to explain the increased blood flow in warm CRPS. With today's knowledge, it makes more sense to relate this increased blood flow to inflammation. Cold CRPS was thought to be caused by an increase in α-adrenergic receptors because of the depletion of local catecholamines. As previously described, the upregulation of α-adrenergic receptors can also be explained by continuing inflammation. The motor system may also be affected.[16] A decrease in the range of motion is common and cannot always be explained by pain alone but is also likely to be of spinal or supraspinal origin. Severe dystonia may occur, characterized by flexion of the fingers, wrist, elbow, and sometimes shoulder, and plantar flexion or extension of the foot. This is typical of a more chronic phase. Since dystonia responds to intrathecal administration of baclofen, spinal γ-aminobutyric acid (GABA) receptors are likely to play a role in its development.

Central Mechanisms

Functional MRI has shown that in CRPS patients, a reorganization can occur in the cerebral cortex.[17] Possibly altering blood flow to the thalamus plays a role, resulting in changes in activation patterns and sensory mapping.

It has been frequently suggested in the past that CRPS is an imaginary disease that typically occurs in women who somatize and have secondary gains because of chronic disabilities. In a systematic review of the literature, Beerthuizen et al. refuted this view and demonstrated that a link between psychological and/or psychiatric determinants and the development of CRPS could only be found in poorly conducted research and not in methodologically sound research.[18] A potentially important explanation for this misconception is that CRPS is regularly used as an embarrassment diagnosis. Another reason is that the natural course of a chronic pain syndrome such as CRPS easily gives rise to anxiety, depression, and catastrophizing. Therefore patients with chronic CRPS can also develop such symptoms. The cause and effect should not be confused.

Certain experiences and/or behaviors can influence the course of CRPS. Extreme fear of pain can lead to kinesiophobia and disuse. Therefore immobilization of the affected extremity takes longer than necessary, the blood flow decreases, and the final result is increased rigidity and muscle atrophy. This was confirmed in a study in which the forearm of healthy volunteers was immobilized with a plaster splint.[19] This immobilization has been shown to cause various symptoms of CRPS, such as temperature changes and changes in mechanical and thermal sensitivity. It is striking that the participants had no pain. The symptoms disappeared after the cast was removed. Several activation mobilization treatments have been developed for this mechanism that can play a role in CRPS, varying from regular physiotherapy to graded exposure.

Interactions Between the Different Mechanisms

CRPS appears to be the result of a complex cascade. The trigger is usually tissue or nerve damage. This leads to sterile inflammation, which is initially physiologic. For unclear reasons, this inflammation runs out of control and does not normally stop after healing. Continuing inflammation leads to spinal and supraspinal changes in sensory and motor skills. Continuing inflammation can also lead to endothelial dysfunction, an increase in α receptors, and small fiber neuropathy. In many patients, inflammatory symptoms are prominent in the early stages. Often, but not always, these symptoms disappear over time, and neuropathic/nociplastic, vasomotor, and/or motor dysregulation become more prominent. However, there are also patients in whom the affected extremity is cold from the start.

In this respect, patients with CRPS can be divided into subtypes, although this is difficult because there is a lot of overlap. Such a classification is relevant because it makes the treatment more mechanically oriented and better tailored to the individual patient. Bruehl distinguished several subtypes in a cluster analysis:[20]

- a relatively limited syndrome in which vasomotor symptoms are prominent
- a relatively limited syndrome in which neuropathic/nociplastic pain and/or sensory disturbances are prominent
- a profuse CRPS syndrome in accordance with the classic description

An important question remains as to why some develop and others do not get CRPS and, even more remarkably, how someone who has experienced major trauma does not advance to the pain syndrome while others progress into a thunderous CRPS after minor trauma. The process is likely determined by a combination of intrinsic factors, such as genetic susceptibility or an autoimmune disease that is acquired or not, extrinsic factors such as the type of trauma and treatment, and environmental factors.

Epidemiology

Various studies have reported different incidence rates for the general population in different studies. A North American study found an incidence of 5.5/100,000 person-years.[21] A Dutch study noted, depending on the diagnostic evaluation strategy used, an incidence of 20 to 26.2/100,000 person-years.[22] This discrepancy may result from differences in population characteristics (ethnicity, rural versus urban), in social, no-life, or health insurance, and in how the diagnosis is defined and classified. The Dutch data show that CRPS occurs more often in the upper extremity and that a fracture is the most common cause. There was no relationship between the severity of initiating trauma and the risk of developing CRPS. CRPS can develop at any age; the peak is between 50 and 70 years of age.

The incidence in women is 3.4 times higher than that in men. Several case reports have described the frequent co-occurrence of CRPS and chronic inflammatory diseases such as amyotrophic lateral sclerosis and Ehlers-Danlos disease. There is some evidence that autoimmunity plays a role in the pathophysiology of CRPS. Several case reports and small observational studies suggest an association between CRPS and previous exposure to certain viruses and bacteria, such as parvovirus B19.[23] About 35% of CRPS patients have autoantibodies against sympathetic neurons, mesenteric plexus neurons, and differentiated cholinergic neuroblastoma lines.

There are indications of a possible genetic predisposition to CRPS. Associations have been found with different polymorphisms of human leukocyte antigen (HLA) and with a TNF-α polymorphism.[24] The findings regarding the role of an ACE gene are contradictory. CRPS is more common in certain families. The prognosis of this condition remains unclear. In a Dutch study of patients with an average disease duration of 5.8 years, three-quarters of the participants still reported sensory and motor trophic disturbances, and some people still had vasomotor and sudomotor complaints.[25]

Clinical Features

The clinical presentation of CRPS is heterogeneous and may vary over time in the same patient.

Medical History

The condition often develops distally in one extremity. The affected area was often more extensive than the original damage. The complaints are characterized by a combination of pain, sensory, vasomotor, sudomotor, motor, and trophic symptoms. The pain is continuous.

TABLE 35.1 New IASP Criteria[26]

1. Continuous persistent pain that is disproportionate to the severity of an injury
2. From at least three of the following four categories, one symptom must be reported by the patient:
   - sensory: hyperesthesia and/or allodynia
   - vasomotor: temperature asymmetry, skin color changes, and/or skin color asymmetry
   - sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry
   - motor/trophic: reduced range of motion and/or motor dysfunction (weakness, tremor, dystonia)
3. From at least two of the following categories, one symptom must be demonstrated at the time of evaluation:
   - sensory: evidence of hyperalgesia (pinprick) and/or allodynia (light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - vasomotor: evidence of temperature asymmetry (>1°C) and/or skin color changes and/or skin color asymmetry
   - sudomotor/edema: evidence of edema and/or changes in perspiration and/or perspiration asymmetry
   - motor/trophic: evidence of a reduced range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
4. There is no other diagnosis that better explains the symptoms

The criteria in Table 35.1 apply for clinical purposes. For research purposes, the diagnostic decision rule is that it is anamnestic in each of the four at least one symptom is identified, and at the physical examination, at least one symptom in two or more categories.

The skin is hypersensitive to touch. Asymmetry can occur in temperature, color, edema, and/or sweating. Sometimes the range of motion is decreased, and sometimes there are motor impairments such as weakness, tremor, or dystonia. Changes in hair and/or nail growth may also occur. Often, the symptoms are not constant over time. CRPS can worsen with the exertion of the affected extremities.

The diagnosis of CRPS is based on these criteria. The criteria most commonly used today were originally initiated by Harden and Bruehl.[26] These were later called the Budapest criteria. After acceptance by the IASP, they are referred to as the new IASP criteria for CRPS. (See Table 35.1.)

Physical Examination

Vasomotor, sudomotor, and trophic signs may be present on inspection. There may be a difference in skin color, edema, hair, and nail growth between the affected and unaffected extremities. Sensory and vasomotor symptoms may be present on palpation. There may be allodynia, hyperalgesia, and skin temperature differences between the affected and contralateral extremities. Motor abnormalities such as loss of function, loss of strength, stiffness, and pain, involuntary movements, tremor, and dystonia may occur during motor function tests.

There are no specific clinical tests for the diagnosis of CRPS. Additional neurologic examination of sensitivity, strength, and reflexes did not reveal any other abnormalities besides the abnormalities previously mentioned.

Additional Research

Several additional studies are possible, but none are pathognomonic.[27] Sometimes supplemental testing is necessary to rule out other diagnoses. Several methods have been developed to classify

and quantify the clinical signs and symptoms of CRPS. These can be used in the context of research or to assess whether a patient meets the CRPS criteria. However, they have no additional value for clinical diagnosis. Examples are:

- infrared temperature measurements

Quantitative Sensory Tests

Volumetry and finger diameter in edema of the extremities

Differential Diagnosis

Many symptoms that can occur with CRPS also occur under other conditions. Therefore CRPS has an extensive differential diagnosis (see Table 35.2).[28] In addition to inflammation, neuropathic, myofascial pain syndromes, degenerative disorders, vascular disease, and psychogenic disorders can be distinguished.

TABLE 35.2 Differential Diagnosis of CRPS[4]

Neuropathic pain syndromes
Peripheral polyneuropathy
Nerve entrapment
Radiculopathy
Postherpetic neuralgia
Post-CVA deafferentation pain
Myofascial pain syndromes
Overload
CANS
Disuse
Fibromyalgia
Non-specific myofascial pain
Degenerative disorders
(Pseudo) osteoarthritis
Chronic tendinopathy
Malposition or pseudoarthrosis after fracture
Inflammation
Epicondylitis
Bursitis
Tendonitis
Erysipelas
Seronegative arthritis
Rheumatoid arthritis
Vascular disease
Thrombosis
Atherosclerosis
Acrocyanosis
Raynaud's phenomenon
Erythromelalgia
Charcot's disease
Psychogenic disorders
Somatoform disorder
Munchhausen syndrome

CANS, Complaints of arm, neck, and/or shoulder; *CVA*, cerebrovascular accident.

Treatment

Many different therapies are used in CRPS, but most have not been proven to be effective. One problem is that treatment targeting one of the mechanisms involved usually treats only part of the pathophysiology. Treatment outcomes can be improved if patients are divided into subgroups. The choice of therapy should be guided by the symptoms most prominent in a particular patient.

A common assumption is that the sooner the therapy starts, the better the result will be. This has never been demonstrated, but it seems likely that persistent inflammation will lead to damage: the sooner treatment starts, the less damage the disease can cause. Also widely accepted is the idea that CRPS patients, especially if they have had the disease for a long time, benefit most from multidisciplinary treatment combining pharmacotherapy, invasive techniques, physiotherapy, occupational therapy, and psychotherapy.

The individual treatments can be divided into anti-inflammatory, activation of mobilization, analgesic, vasodilating, spasmolytic, and psychological treatments. Generally, one will start with more conservative treatments and move to invasive treatments only after conservative treatment has failed.

Anti-Inflammatory Treatment

Dimethyl Sulfoxide and N-Acetyl-L-cysteine

Oxygen radical scavengers, such as dimethyl sulfoxide (DMSO) and N-acetyl-L-cysteine (NAC), appear to have a positive effect. Intravenous mannitol did not have any effect.

DMSO and NAC are excellent therapies in European countries, especially the Netherlands. However, the use of these drugs is much less in other parts of the world.[29]

Immune Modulating Drugs[21]

Corticosteroids

Corticosteroids have been shown to be effective in small studies, but their efficacy in practice remains limited. Side effects, in particular, require great restraint.[30]

TNF-α Inhibitors

TNF-α is a pro-inflammatory cytokine. Thus the effect of anti-TNF probably relies on the inhibition of the inflammatory cytokine cascade. The literature contains two case reports and one report of a prematurely terminated randomized control trial (RCT).[31–33] The case reports show a favorable effect. The provisionally terminated RCT did not provide a clear conclusion regarding the place of this therapy. Thalidomide inhibits monocyte TNF-α production thalidomide had a favorable outcome in two case reports and open-label studies.[34–36] Lenalidomide is a third-generation thalidomide. An RCT did not show any beneficial effects.[37] The adverse effects were serious.

Bisphosphonates

Bisphosphonates influence the production of pro- and anti-inflammatory cytokines. The literature contains four double-blind RCTs.[38–41] The RCTs examined the effects of oral or intravenous alendronate, clodronate, and pamidronate and found a significant reduction in pain.

Immunoglobulins

The mechanism of action of immunoglobulins is based on complex interference with the immune system. The literature contains a double-blind RCT, which compared intravenous immunoglobulin with placebo, the pain intensity in the treatment group decreased 1.55 units more on an 11 point numeric scale than in the placebo group.[42]

Activation and Mobilization

Fear of pain can lead to kinesiophobia (fear of physical movement and activity), disuse, prolonged immobilization of the affected extremity, and eventually rigidity and muscle atrophy.[43] Physiotherapy has a positive effect on the patient's activity level, reduces edema, improves blood flow, prevents muscle atrophy, contractures, and fear of movement, and promotes functional recovery. It is recommended to prescribe activation and mobilization therapy in all patients with CRPS.

Analgesia

Pain in CRPS can be the result of several underlying mechanisms. Inflammation causes nociceptive pain, and vasomotor disorder causes ischemic pain, which is mixed nociceptive and neuropathic; central sensitization causes nociplastic pain. Additionally, thin fiber neuropathy and, the underlying lesion of the somatosensory system in CRPS 2 will cause neuropathic pain. Dystonia and contractures cause nociceptive pain. Based on the underlying and predominant pain category (nociceptive, nociplastic, neuropathic), a choice can be made from one or a combination of painkillers.

The efficacy of individual analgesics in patients with CRPS has also been studied. Only a minor effect of gabapentin and S-ketamine has been demonstrated.[44,45] No effect has been shown for other drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, other anti-epileptics, and anti-depressants. It is conceivable that there is a place for these drugs, but especially when prescribing NSAIDs and opioids, care must be taken with close monitoring for side effects and preferably only for the short term.

Vasodilation

There is evidence that local application of NO via an isosorbide dinitrate ointment 1% or 2% and/or a phosphodiesterase inhibitor is effective in patients with endothelial dysfunction with NO and endothelin-1 imbalance.[46]

Autonomic dysfunction and/or ongoing inflammation increase the number of α receptors. Calcium blockers, such as verapamil, can be effective.[47,48] Ketanserin intravenously appears to be effective.[49] Based on this, it is also prescribed orally, but the effectiveness of this route has not been proven.

Spasmolytic Therapy

Based on the observation that intrathecal baclofen can be effective in the treatment of dystonia in CRPS, the GABA system is believed to play a role. From the recommendation that we first start as conservatively as possible, oral antispasmodic therapy with benzodiazepines (diazepam or clonazepam) or baclofen is prescribed, but unlike the intrathecal administration of baclofen, there is insufficient evidence supporting the effectiveness of this route.[50] Although widely used, there is also no evidence of the efficacy of botulinum toxin A for the treatment of dystonia in CRPS patients.[51]

Psychological Counseling, Pain Management, and Rehabilitation Therapy

If components of perception or behavior perpetuate the clinical picture or cause much suffering, psychological treatment or a pain management program can be valuable. Disability in CRPS is the sum of the damage and disability.

Invasive Treatments

Several invasive treatments are available. In general, it is advisable to start with more conservative methods and start with more invasive therapies if the patients are refractory. The efficacy of invasive pain therapies has recently been summarized in an update of the evidence-based guidelines on invasive pain treatment.[52]

Sympathetic blocks

The application of sympathetic blocks is based on the idea that autonomic nervous system dysfunction and an increase in α receptors play a central role in CRPS. It is also believed that a pathologic connection may arise between the somatosensory system and the sympathetic system, causing sympathetic mediated pain.

Intravenous Block With Guanethidine

Intravenous sympathetic blockade with guanethidine has been widely used in the past, based on the idea that guanethidine depletes norepinephrine in nerve endings.

There is moderate evidence that intravenous regional blocks with guanethidine for the treatment of CRPS do not provide better pain relief than placebo at one, three, and six months.[53]

Blocks of the Sympathetic Chain

There are several ways to block the sympathetic ganglion: with a local anesthetic (repeated or not), with a neurolytic agent such as alcohol or phenol, botulinum toxin, or radiofrequency lesion. While it has been widely advocated and practiced in the past, the evidence is disappointing.

Sympathetic Blocks With Local Anesthetics

There is conflicting evidence that sympathetic blocks are effective. A Cochrane review showed moderate evidence that sympathetic blocks with a local anesthetic at the cervical and lumbar levels are ineffective for the treatment of complex regional pain.[54] However, there is low quality evidence showing that thoracic sympathetic blocks (T2-3) with ropivacaine and triamcinolone reduce pain significantly better in patients with upper extremity CRPS than a subcutaneous injection 12 months after treatment.[55] A more recent retrospective study showed very low quality evidence that sympathetic blocks with local anesthetics (with or without corticosteroids) to be effective (greater than 50% relief) in 61% of patients (155 of 255), with relief lasting one to four weeks or longer. In this study, the Budapest criteria were used, and the sympathetic blocks consisted of either stellate ganglion blocks, T1-T3 sympathetic blocks, or L2-L4 for lumbar sympathetic blocks.[56] They also noted that the effects of sympathetic blocks did not predict the success of spinal cord stimulation. There seems to be a place for sympathetic blockades, especially because of the minimal invasiveness of the treatment, the low cost, and the lack of more conservative alternatives. Further research is necessary, especially focusing on predictors of outcomes.

Neurostimulation

Neurostimulation is a direct clinical application of the gate-control. Primarily, it is used to treat neuropathic pain, but with stimulation of the spinal cord and stimulation of the DRG, there are additional effects on the vasomotor disturbance and possibly inflammation, as well as stimulation of the DRG on motor dysfunction. This is probably why spinal cord stimulation and spinal ganglion stimulation are among the most effective treatments for CRPS. Neurostimulation has simultaneous effects on the multiple mechanism which can play a role in the pathophysiology of CRPS.

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is widely used. However, there is no evidence to suggest that TENS is effective.

Spinal Cord Stimulation (SCS)

There is moderate evidence that SCS reduces pain in patients with complex regional pain syndrome.[57] A randomized placebo-controlled study with 29 CRPS patients was found to have a statistically and clinically significant effect on pain for different stimulation modes than a placebo after a two week test period.[58]

DRG Stimulation

A randomized controlled trial (ACCURATE study)[59] demonstrated the superiority of DRG stimulation over conventional SCS stimulation at three and 12 months of follow up in patients with lower extremity CRPS.

Peripheral Nerve Stimulation

There is evidence of very low quality that in CRPS, peripheral nerve stimulation effectively reduces pain during long term follow up and reduces pain-related disability.[60]

Intrathecal Baclofen

If conventional spasmolytic treatments are ineffective, baclofen can be considered intrathecally. It is a technically complex treatment with many potential side effects.[61]

Prophylaxis

In an RCT, it has been shown that vitamin C has a protective effect against the development of CRPS-1 after wrist fractures.[62] If a person with a history of CRPS has new trauma or requires surgery on an extremity, prophylactic therapy with vitamin C may be considered. Vitamin C can be administered during the perioperative period.

Summary

CRPS is a complication of tissue and/or nerve damage. Multiple pathophysiologic mechanisms, including autoinflammation, sensory, vasomotor and sudomotor, and motor/trophic disorders, may play a role simultaneously. Depending on the most prominent mechanism, different phenotypes can be distinguished. Treatment appears to be the most effective when it is mechanism oriented.

Key Points

- Several mechanisms contribute to the development of the CRPS. These include afferent mechanisms such as inflammation and endothelial dysfunction, efferent mechanisms such as changes in the somatosensory and autonomic nervous system, and central mechanisms, including cortical reorganization and psychological factors.
- Subtypes of CRPS include a relatively limited syndrome in which vasomotor symptoms are prominent, a relatively limited syndrome in which neuropathic/nociplastic pain and/or sensory disturbances are prominent, and a profuse CRPS syndrome in accordance with the classic description.
- The commonly used criteria for CRPS are the Budapest criteria, now referred to as the new IASP criteria for CRPS.
- Many therapies have been used in CRPS, but their effectiveness has not been proven. This is because the treatment targets one of the mechanisms involved, treating only a part of the pathophysiology. The choice of therapy should be guided by the symptoms most prominent in a particular patient.
- The individual treatments can be divided into anti-inflammatory, activation of mobilization, analgesic, vasodilating, spasmolytic, and psychological treatments.
- One usually starts with more conservative treatments and move to invasive treatments after conservative approaches have failed.
- Of the anti-inflammatory pharmacologic medications, biphosphonates appear to be effective.
- Physiotherapy has a positive effect on the patient's activity level, reduces edema, improves blood flow, prevents muscle atrophy, contractures, fear of movement, and promotes functional recovery.
- Oral antispasmodic therapy with benzodiazepines (diazepam or clonazepam) or baclofen was attempted. Unlike the intrathecal administration of baclofen, there is insufficient evidence regarding the effectiveness of the oral route. Intrathecal baclofen is technically complex and has many potential side effects.
- Sympathetic blocks with local anesthetics have not been uniformly effective.
- There is moderate evidence that SCS reduces pain in patients with CRPS.
- There is initial evidence of the superiority of DRG stimulation over conventional SCS in patients with lower extremity CRPS.
- There is very low quality evidence that peripheral nerve stimulation effectively reduces CRPS pain and diminishes pain-related disability.

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36

Evaluation and Treatment of Pain in Selected Neurologic Disorders

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Pain in Selected Neurologic Disorders

Although chronic pain may be the defining feature of certain neurologic disorders, physicians often focus on treatments aimed at addressing the primary neurologic condition. As most comorbidities may come from pain associated with the condition, it should be addressed early during treatment. Chronic pain is a three-dimensional process consisting of biologic, psychological, and social components. All three interact dynamically and affect the states of the others. Here, we provide a basic pathophysiologic explanation of pain that accompanies these conditions and treatment strategies to complement disease-based treatments and improve the quality of life of affected individuals. Although it is not possible to include every disorder in which pain is a feature, this chapter discusses the pertinent features of diseases that pain specialists are likely to encounter with some frequency (see the reference list for detailed reviews of each disorder in the literature, when available). We focused on the evaluation, diagnosis, and treatment of neuropathies due to peripheral nerve, spinal cord, and brain pathologies (Table 36.1). Chapter 34 discusses complex regional pain syndrome (CRPS); postherpetic neuralgia and diabetic peripheral neuropathy are addressed in Chapter 33. More details on neuroanatomy and pathophysiology can be found in Chapters 8 and 9.

Peripheral Neuropathies

Most instances of painful peripheral neuropathies are acquired and can be divided into metabolic, autoimmune, infectious, traumatic, iatrogenic, and idiopathic etiologies (Table 36.2). Evaluation begins with a medical history, physical and neurologic examinations, and laboratory tests. Nerve conduction studies (NCS), electromyography (EMG), autonomic function assessment, cerebrospinal fluid analysis (CSF), magnetic resonance imaging (MRI), and biopsy may be included.

The Workup

To differentiate among the different types of neuropathies, a detailed history must be obtained. Specifically, the time course, presence and characteristics of sensory, motor, and autonomic symptoms, the distribution of symptoms (proximal and/or distal, hands and/or feet, symmetric/asymmetric), and intensity must be assessed. Medical history, social history, family history, medications, and exposure to toxins must be considered. The duration of symptoms is important in categorizing neuropathy into acute (<4 weeks), subacute (4–12 weeks), and chronic (>12 weeks). Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome [GBS]) peaks at four weeks of onset, and progression beyond eight weeks suggests chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Based on their distribution, neuropathies can be categorized as mononeuropathy (single peripheral nerve involvement, usually due to trauma, compression, or entrapment), mononeuropathy multiplex (multiple, separate noncontiguous peripheral nerves either simultaneously or sequentially, commonly due to systemic vasculitis), and polyneuropathy (toes and soles are affected first and hands later, usually due to metabolic, toxic, or systemic disorders).

Sensory symptoms include positive (burning, pain, walking on cotton wool, band-like sensation on the feet or trunk, stumbling, tingling, pins and needles) and negative symptoms (numbness, loss of sensation) in the hands and feet. Motor symptoms include weakness and fine motor difficulties (e.g. unfastening a button and opening bottles). Autonomic symptoms, such as postural hypotension, impotence, sphincter disturbance, diarrhea, constipation, dryness, and excessive sweating, point to the involvement of small myelinated or unmyelinated nerve fibers.[1]

Medical history should look for systemic diseases that can be associated with neuropathy, such as diabetes, hypothyroidism, chronic infections, and/or autoimmune diseases. Aside from chemotherapeutic agents that may cause polyneuropathy, commonly used medications associated with polyneuropathy include pyridoxine (vitamin B6), phenytoin, linezolid, metronidazole, nitrofurantoin, isoniazid, chloramphenicol, dapsone, reverse transcriptase inhibitors, amiodarone, colchicine, and disulfiram.[1] Family history should include ethnic background, consanguinity, and details about parents and siblings, such as the presence of high-arched feet, flatfeet, hammertoes, gait dysfunction, bilateral carpal tunnel syndrome, and other signs of possible inherited neuropathies.[2] Social history includes the patient's country of origin, potential occupational exposure, potential exposure to people with transmittable illness, alcohol and drug use, and travel history.[3] Psychosocial assessment should be performed for depression, anxiety, personality disorders, substance use, and cognitive deficit comorbidities.[4]

Neurologic examination should include examination of cranial nerves, muscle power, tone, and reflexes, detailed evaluation

TABLE 36.1 Pain Syndromes in Neurologic Disorders

Primary Disorder	Pain Location	Pain Classification and Descriptors	Etiologies
Peripheral neuropathy	Stocking-glove distribution	**Neuropathic** Burning, tingling, stabbing, dysesthesias	• Metabolic (diabetes) • Autoimmune (vasculitis) • Idiopathic (trigeminal neuralgia, small fiber) • Infectious (postherpetic) • Trauma • Iatrogenic (chemotherapy) • Other
Spinal cord disorders	Radicular, transitional zone pain, deafferentation pain, musculoskeletal pain (shoulders), spasticity related pain (lower limbs), abdomen (visceral)	**Neuropathic** Constant burning, tingling, aching, evoked shooting pain **Nociceptive** Aching, dull **Visceral** Dull, cramping,dysreflexia, autonomic dysfunction	• Infectious • Trauma (SCI) • Tumor • Demyelination (MS) • Vascular (stroke, malformations) • Other
Brain and brainstem lesions	Contralateral extremities, ipsilateral face (brainstem)	**Neuropathic** Aching, burning, dysesthesias, sharp **Spasticity related** **Musculoskeletal**	• Vascular (stroke, malformations) • Neurodegenerative • Demyelination • Trauma (TBI) • Other

TABLE 36.2 Painful Peripheral Neuropathies

Classification by Cause	Examples
Metabolic disorders	Diabetes mellitus, vitamin deficiency (thiamine, vitamin B12), uremia
Toxins	Ethanol, heavy metals (arsenic, lead), industrial solvents
Drug induced	Chemotherapy, isoniazid, antiretroviral therapy
Trauma	Complex regional pain syndrome type 2, neuromas, postamputation pain, peripheral nerve trauma
Entrapment	Peroneal, ulnar, median (carpal tunnel syndrome), posterior tibial (tarsal tunnel syndrome)
Autoimmune	Connective tissue disorders, vasculitis, paraneoplastic disorders, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy
Infectious	Lyme disease, spirochetal infection, herpes zoster, cytomegalovirus infection
Hereditary	Familial amyloid polyneuropathy, Fabry's disease

of all sensory modalities (pinprick, pain, temperature, vibration, and joint position), and an observation of the patient's gait and the ability to stand up from a chair. Specific findings include anosmia (as in B12 deficiency), impaired pupillary light reflex (diabetes, GBS), ophthalmoplegia (GBS), and widespread reflex loss, including muscles that are not particularly weak or wasted, favoring demyelinating neuropathy. In contrast, selective loss of ankle reflex in the presence of distal wasting and weakness is characteristic of axonopathy.[2] Meticulous general physical examination can identify several clues for diagnosis, nail changes (Mee's lines) in toxin poisoning (such as arsenic and thallium), musculoskeletal abnormalities, such as pes cavus, high-arched feet, and mutilation (usually hereditary neuropathy), skin changes, or nerve thickened nerves in rare diseases.

Following history and examination, chronic, distal, slowly progressive, symmetric, predominantly sensory polyneuropathy can be diagnosed clinically without further testing. If any atypical feature is noted in the initial or subsequent evaluation, including asymmetry, severe early sensory complaints such as ataxia and loss of proprioception, early or severe pain, the predominance of or early motor involvement, proximal symptoms, and fast progression, neurophysiologic testing should be pursued. Similarly, other than a classic presentation of acute GBS, all other acute neuropathies should be further evaluated.

The clinical evaluation includes evaluation of complete blood count (CBC), erythrocyte sedimentation rate (ESR), fasting glucose or glucose tolerance test, liver and renal function tests, serum vitamin B12 and folate levels, thyroid function tests, serum protein electrophoresis, and immunofixation electrophoresis. The vasculitis profile (antinuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, extractable nuclear antigen, anti-Ro, anti-La) is added when patients suffer from related complaints, such as joint pain or Sicca syndrome. Human immunodeficiency virus (HIV), hepatitis B and C, and Lyme tests should be added based on risk factors or previous exposure. In case of alcohol abuse, malnutrition, absorption abnormalities, or vitamin toxicity, methylmalonic acid (especially when borderline B12), homocysteine (especially when borderline B12), pyridoxine (vitamin B6), thiamine (vitamin B1), and vitamin E should be evaluated. Heavy metals, including copper and zinc, can also be checked for patients with an exposure history. Sarcoidosis can be evaluated using serum or CSF angiotensin-converting enzyme, although the specificity

is limited. Paraneoplastic markers, such as anti-Hu, can be added based on clinical suspicion and previous workup.

For acute neuropathy, laboratory work should mainly include infections (West Nile virus, Hepatitis B, C, Rabies, HIV, CMV, Lyme, ESR, and CRP), heavy metal levels (arsenic, thallium, and lead), inflammatory panel (antinuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, cryoglobulins), serum and urine paraproteins, urine porphobilinogen, and urine porphyrin excretion for porphyria evaluation.[5]

In many cases, NCS of sensory and motor nerves, late responses (F response and H reflex), and needle EMG are performed. These tests do not provide information regarding the cause of neuropathy but enable the determination of the type (demyelinating vs. axonal) and localize the lesion more precisely than on clinical examination alone. This is valuable mainly in acute neuropathies,[6] asymmetric neuropathies, and mononeuropathies. The classic demyelinating neuropathy findings include slowing of nerve conduction velocity, prolongation of terminal latency (F latencies), temporal dispersion, and prolonged compound muscle action potential (CMAP) or conduction block (decline in the compound muscle action potential exceeding 20% on proximal stimulation compared to that on distal stimulation). Axonal neuropathy usually shows mild slowing of nerve conduction (due to sparing of remaining axons), reduced CMAP amplitude, and fibrillations on EMG. Sensory nerve action potentials and sensory conduction velocities are reduced in both axonal and demyelinating neuropathies. However, sensory conduction studies evaluate only fast-conducting fibers, which may be normal in selective small fiber and autonomic neuropathies.[3] Thus NCS and EMG tests are mainly useful for large fiber peripheral neuropathies rather than small fiber neuropathies.

CSF analysis is indicated in acute neuropathies for GBS evaluation, and it is useful in chronic inflammatory demyelinating polyneuropathy and chronic immune-mediated axonal neuropathies where the levels of CSF protein are elevated. Significant pleocytosis can suggest other acute inflammatory neuropathies, such as Borrelia, sarcoidosis, and HIV. Nerve biopsy, usually taken from the sural nerve, remains the primary method of establishing vasculitis neuropathy when histology is unavailable elsewhere. Combined nerve and muscle biopsies are recommended to improve the diagnostic yield. The yield of biopsy in the diagnosis of chronic axonal neuropathies is very small and not justified when vasculitis is unlikely.[3] Skin biopsy allows for the quantification of somatic and autonomic small nerve fibers. Small fiber neuropathy is diagnosed when intraepidermal nerve fiber density falls below age- and sex-adjusted normative reference values.[7] Fine-needle aspiration biopsy of the abdominal fat pad with Congo red staining is a minimally invasive procedure used to demonstrate tissue deposits of amyloid in patients with neuropathy related to amyloidosis.

In the case of autonomic neuropathy, bedside autonomic tests include blood pressure response to standing or vertical tilt (normal fall, <20/10 mm Hg), heart rate response to standing (increase, 11–90 beats/min), heart rate variation with respiration (normal, ≥15 beats/min, inspiratory expiratory ratio 1.2), cold pressure test (after 1 min, increase in systolic blood pressure of 15–20 mm Hg, diastolic 10–15 mm Hg). Other tests may include quantitative sudomotor axon reflex sweat test (applying electrical stimulation to introduce acetylcholine into the skin, with subsequent measurement of the volume of sweat produced), pupillary tests, Schirmer's test, and sympathetic skin response. When hereditary etiology is suspected based on age, time course, and/or family history, genetic testing can be performed for Charcot-Marie-Tooth, amyloidosis, distal hereditary motor neuropathy, Friedrich's ataxia, and others.

The Differential Diagnosis

Autoimmune Causes

Autoimmune neuropathies may result from connective tissue diseases, vasculitis, and autoimmune disorders of the peripheral myelin. Neuropathic pain may precede diagnosis or occur during an established disease. Mononeuropathy multiplex is characterized by pain, numbness, and weakness in the distribution of peripheral nerves, most commonly the ulnar, median, and peroneal nerves. Dysfunction typically occurs at common sites of nerve entrapment. Another presentation is distal symmetrical polyneuropathy (DSP). DSP is characterized by numbness, tingling, and pain in a characteristic symmetric stocking-glove distribution. Symptoms typically begin in the feet and include burning, aching, and dysesthesia. Asymmetry of progression is a hallmark of the disease.

Acute inflammatory demyelinating polyneuropathy, known as Guillain-Barré syndrome, occurs at an annual incidence of approximately 1.11/100,000 person-years, with a 20% increase every decade after the first decade of life.[8] GBS may develop during the initial manifestation of HIV seroconversion. Paresthesia or dysesthesia typically precedes the development of weakness, which proceeds in an ascending pattern (distal to proximal). Clinical diagnostic criteria for GBS include relatively symmetrical weakness with decreased or absent tendon reflexes. Symptoms reach maximal intensity within four weeks of onset, and other possible causes must be excluded. A high level of protein in the CSF is suggestive.

Contemporary treatment strategies with intravenous immunoglobulins, plasmapheresis, and other agents have limited the disability associated with the disorder, but a small proportion of patients may have disability and chronic pain. Pain is often a prominent symptom during the acute phase of the illness. Deep aching and throbbing pain in the lower back region associated with radiation into the lower extremities is typically the most excruciating and disabling pain. A positive straight leg raise test may also be performed. Myofascial pain may coincide with the development of muscle spasms, cramps, and muscular tenderness. Stabbing, shock-like, or electric pain may be present in the extremities and face. Ectopic impulses caused by acute nerve root inflammation may be the pathologic mechanism associated with the acute neuropathic pain component in GBS. Chronic neuropathic pain may persist beyond treatment and recovery from paralytic disorders in a small proportion of patients.[9] The autonomic nervous system dysfunction present in GBS may lead to the development of headaches, cardiovascular instability, visceral pain secondary to ileus, and urinary retention.

Infectious. Peripheral neuropathic pain is a common accompaniment of HIV. It is estimated that 35% of patients infected with HIV experience symptomatic DSP.[10] Neuropathic pain may complicate any stage of the infection and result in disordered sleep and ambulation, disability, and psychosocial distress. Acute polyneuropathy associated with seroconversion typically resolves with mild, if any, residual sequelae of neuropathic pain. In the intermediate to late stages of the disease, chronic inflammatory polyneuropathy, distal symmetric HIV-induced sensory axonal polyneuropathy, and vasculitic mononeuropathy multiplex may appear. Chronic inflammatory polyneuropathy manifests as neuropathic pain associated with severe sensory loss, weakness, and gait disturbance. Distal symmetric HIV-induced sensory axonal polyneuropathy manifests as burning pain, numbness, allodynia, and evoked dysesthesia beginning in the lower extremities, with variable progression to the upper extremity. They often persist despite treatment of the primary disease.

Infections during the illness, especially if untreated or refractory to treatment, such as neurosyphilis, herpes simplex virus, and toxoplasmosis, may contribute to neurologic symptoms. Cytomegalovirus infection may give rise to progressive polyradiculopathy, mononeuropathy multiplex, or both. Polyradiculopathy is characterized by the development of pelvic and lower extremity radicular pain and urinary retention and may progress to cauda equina syndrome.[11]

Besides the neuropathies associated with primary HIV infection, antiretroviral agents may be neurotoxic. The dideoxynucleoside family of nucleoside analog reverse transcriptase inhibitors has been shown to have specific peripheral neurotoxic effects.[12] Antiretroviral-induced neuropathies are manifested by distal dysesthesias, burning, tingling, and shooting pains and are more rapidly progressive and more painful than HIV polyneuropathy. Antiretroviral polyneuropathy occurs in 26%–66% of patients, but the symptoms often improve with drug cessation or reduction.[10] The antiepileptic drug lamotrigine has been shown to be beneficial in refractory cases.[13]

Lyme disease is a multisystem disorder caused by several Borrelia subspecies bacteria that are transmitted by infected ticks. A history of a tick bite, especially when the patient has been in the northern, mid-Atlantic, and north-central regions of the United States, is common. Patients may also show a ring-like skin lesion at the site of the bite and flu-like symptoms.[14] Within days to weeks, a disseminated infection may affect the skin, nervous system (neuropathy, headaches, cognitive deficits, sleep disorder, fatigue), heart (conduction blocks), or joints. Diagnosis is confirmed by serology or polymerase chain reaction on suspected lesion skin biopsy. It is distinguished from other neurologic disorders as it is transferred focally, and there is no evidence of multiple sclerosis or demyelinating disease.[15]

Appropriate antibiotics are mandated. However, more than 16%–18% of antibiotic-treated Lyme patients continue to suffer from chronic pain years after diagnosis. Chronic neuropathic pain may be radicular and associated with sensory abnormalities, such as paresthesias.[16] Additionally, in 10% of patients with antibiotic-treated Lyme-arthritis, chronic arthritis develops and is unresponsive to additional antibiotic courses. Nonsteroidal medications are the mainstay of treatment.[17]

Metabolic. Nutritional deficiencies can cause peripheral neuropathies and chronic pain. Thiamine or vitamin B1, vitamin B12, and vitamin B9 (folate) are used for myelination of the central and peripheral nervous system and are necessary for function.[18] Thiamine is responsible for the use of glucose and energy in the central nervous system.[19] B12 and B9 work together to produce methionine from homocysteine. The deficiencies should not be considered independently of one another.[20] Deficiencies of these vitamins lead to demyelination of the spinal cord, cranial nerves, and peripheral nerves, and loss and swelling of the myelin sheath.[18] The prevalence of B12 deficiency varies by age group and affects 3% of young adults and up to 6% of the elderly,[21] whereas folic acid deficiency has been estimated to have a prevalence of 2%.[22] In elderly patients, B1 deficiency is about 5%.[23]

Although the symptoms are largely overlapping, there are more spinal cord and peripheral nerve disorders caused by B12 deficiency, more affective disorders caused by folate deficiency, and additional cardiovascular disorders caused by B1 deficiency.[19,24] Typical symptoms progress symmetrically, including pain, paresthesia, ataxia, spasticity, paraplegia, impaired sense of vibration and proprioception, and progressive weakness.[25,26] In addition, cognitive deficits, hearing loss, macular degeneration, and affective changes including depression can be prominent.[27]

The main source of B9 and B12 intake comes from the consumption of animal products, whereas that of B1 intake comes from meat, whole grain, and fish.[25] Therefore it is important to examine the patient's diet and any digestive issues they may have. Malnutrition, alcoholism, gastric surgery, anemia, malabsorption disorders, pernicious anemia, and gastric acid reduction therapy can all contribute to B12 and B9 deficiencies. Elderly patients are also at a higher risk of developing B12 deficiency.[26] Alcoholism, dialysis, chronic diarrhea, and high doses of diuretics are risk factors for B1 deficiency.

Initial laboratory assessments include CBC, which can show megaloblastic anemia and macrocytosis (mean cell volume greater than 100 femtoliters), serum/plasma folate levels, and B12. For folate deficiency, additional assessments include red cell folate concentrations, whereas B12 deficiency should be confirmed with elevated plasma methylmalonic acid levels. Total plasma homocysteine levels are also indicative of both folate and B12 deficiency.[20] Cervical and thoracic spinal cord MRI T2-weighted sequence may show bilateral posterior column hyperintensities indicating severe myelopathy.[18,28] B1 levels can be measured by thiamine diphosphate using chromatography.[19] Oral or injected administration of the missing factor is recommended as a treatment. Patients with anemia or digestive issues are recommended life-long therapy.[18]

Traumatic. Injuries from motor vehicle accidents, falls, sports, and medical procedures can stretch, crush, or compress nerves or detach them from the spinal cord. Furthermore, less severe traumas, such as broken or dislocated bones, can also cause serious nerve damage. Prolonged pressure on a nerve (such as a cast) or repetitive, forceful activities can cause ligaments or tendons to swell, which narrows the slender nerve pathways. The incidence of traumatic peripheral nerve injury varies from 2.8% to 5% in the population.[29] Chronic postsurgical pain is experienced by 10%–50% of individuals, depending on the type of surgery and surgical technique. It is experienced by 50%–85% of patients after limb amputation, 30%–50% of patients after thoracotomy, and 20%–50% of patients after mastectomy.[30] Medical history, trauma details, and physical examination are usually enough for clinical diagnosis. In cases of peripheral neuroma formation following trauma, classic surgeries including neuroma resection, neurorrhaphy, and nerve stump repositioning can be considered.[31] Peripheral nerve stimulation or spinal cord neurostimulation (SCS) may be options in cases with severe pain or when drug adverse events prevent the continuity of pharmacologic therapies.[32]

Iatrogenic. Neurotoxic cancer treatments, such as platinum compounds, taxanes, vinca alkaloids, thalidomide, and bortezomib, can damage the organization of microtubules in neuronal axons and sensory axons, resulting in neuropathic pain.[33-35] Moreover, 30%–40% of patients treated with neurotoxic chemotherapy develop neuropathic pain.[35] Most chemotherapy-induced neuropathic pain is dose-dependent, and neuropathy develops about two months after the start of treatment.[35] However, with some medications, neuropathy can worsen even with the cessation of chemotherapy. In one study, 30% of 114 lymphoma patients continued to present new symptoms after discontinuation of vincristine administration.[34] Patients developed paresthesia, burning sensations, numbness, autonomic dysfunction in the cardiovascular and digestive systems, and tactile hypersensitivities.[33,34] Some patients also experienced urinary retention, sexual dysfunction, and constipation.[34] Symptoms are typically symmetric and occur in the hands and feet in a stocking-glove distribution.[36]

Although chemotherapy-induced neuropathy is common in oncologic patients, it is important to rule out other causes of neuropathy. Direct neoplastic infiltration can mimic CIDP and can occur in leukemia, neurolymphomatosis, and carcinoma. Graft-versus-host disease from bone marrow transplantation can also cause neuropathy. Certain comorbidities can present a higher risk of chemotherapy-induced neuropathy, such as diabetes.[35] For diagnostic testing, NCS are the best as reduced compound sensory action potentials are associated with chemotherapy-induced neuropathy.

Small Fiber Neuropathy

Small fiber neuropathy results from dysfunction of small diameter peripheral nerve fibers, such as C fibers and Aδ fibers.[37] Worldwide, 53 out of 100,000 people suffer from small fiber neuropathy.[37,38] About 50% of all small fiber neuropathy cases are idiopathic. Symptoms of small fiber neuropathy include pain, paresthesia, allodynia, hyperesthesia, and autonomic and enteric dysfunction such as dry eyes, dry mouth, abnormal sweating, syncope, and gastrointestinal issues.[37,38] The pain is described as burning, shooting, and electric shock-like.[37,38] Patients often have multifocal and widespread pain. However, fibromyalgia patients tend to lack pinpoint tenderness on physical examinations.

Several conditions are associated with small fiber neuropathy, such as diabetes, HIV and hepatitis C infections, B12 deficiency, thyroid dysfunction, chronic inflammatory demyelinating polyneuropathy, Sjogren's syndrome, and GBS.[37,38] Recent studies also show that there may be a relationship between complex chronic pelvic pain, as 64% of patients with complex chronic pelvic pain from referral clinics also tested positive for small fiber neuropathy.[38] Exposure to toxins such as alcohol, thallium, neurotoxic antibiotics, and chemotherapy medications are also associated with the development of small fiber neuropathy.[33,37]

Diagnostic criteria include signs of small fiber damage (pinprick and thermal sensory loss and/or allodynia and/or hyperalgesia) and/or length-dependent symptoms along with low intraepidermal nerve fiber density on skin biopsy from the thigh or distal calf and/or abnormal quantitative sensory testing thermal thresholds in the ankle and foot.[39] Autonomic function tests, such as a quantitative sudomotor axon reflex test, can also be a helpful diagnostic test when combined with other tests. A sural nerve conduction study or electromyography may be used to reject large fiber neuropathy.[37]

Idiopathic Sensory Polyneuropathy

A significant number of patients exhibit symptoms of peripheral neuropathic pain in a characteristic stocking-glove distribution without a definable causative agent. This diagnosis is one of exclusion following a comprehensive evaluation, including history, physical and laboratory tests, NCS/EMG studies, and biopsy. The disorder is estimated to occur in approximately 25% of those aged 65 years and older and in as many as 50% of those aged 85 years and older. In many cases, the disorder is characterized by the loss of peripheral pain and temperature sensation. In a significant proportion of cases, complaints of burning, tingling, and symptoms of restless legs syndrome may be predominant. This syndrome may be associated with difficulty ambulating, falls, and a reduction in quality of life.[40] The symptoms are typically worse at night, leading to disrupted sleep, with therapy aimed at minimizing insomnia.

Pain in Neuromuscular Disorders

Neuromuscular disorders describe a heterogeneous group of neurologic conditions associated with diseases of the peripheral motor nerves, neuromuscular junction, muscles (muscular dystrophies, myopathies), and anterior horn cells. In a large series of patients with post-polio syndrome, a large proportion of patients (80%) reported muscular and joint pain.[41] The common feature in these conditions is the notable loss of muscle power and tone and the presence of muscular atrophy. Syndromes with slow progression over time are characterized by disorders of ambulation, which may lead to chronic disability and incapacitation. With disease progression, concomitant musculoskeletal pain may be associated with the loss of neuromuscular support of the axial spine, pelvic, and shoulder girdles. As is common in other chronic pain syndromes, pain may be associated with significant psychosocial distress, mood, and sleep disorders.

The Treatment of Peripheral Neuropathies

This section will focus on the treatment of pain related to peripheral neuropathies. Attention must be paid to treating the underlying causes. Infectious pathogens should be treated with antibiotics or antiviral agents, as appropriate for specific conditions. Nutritional deficiencies should also be addressed. Systemic autoimmune disorders and specific demyelinating disorders (such as GBS/CIDP) can be treated with steroids and other immunosuppressants, and in some instances, IVIG or plasmapheresis. Neuromodulatory medications may also be utilized. Gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants (TCAs), and capsaicin are the most effective options.[42] Most of these first- and second-line options come with considerable potential for side effects. If the patient does not gain significant relief or has adverse effects from a medication, then dosing should be adjusted and/or alternative therapy may be used or added.[42] The treatment of autonomic neuropathies should not be overlooked. Most cases of orthostatic hypotension can be initially managed with non-pharmacologic treatments, including avoidance of triggers, a head-up tilt of the bed at night, and adequate hydration and compression stockings. Gastroparesis, which can be a significant pain generator, should be managed with supportive measures including small regular meals 4–5 times a day, low-fat and low-residue meals, avoidance of carbonation, alcohol, and tobacco, and optimization of liquid nutrition (Table 36.3).[4]

First Line Agents

Gabapentinoids are traditionally the first agents trialed and include gabapentin and pregabalin. They work by blocking presynaptic α-2-δ calcium channels in the dorsal horn, thereby inhibiting neurotransmitter release.[43] Gabapentin and pregabalin both have been shown to be effective with numbers needed to treat (NNT) of 50% pain reduction of 3.9 (3.3–4.7) in painful polyneuropathy, 4.6 (4.3–5.4) in postherpetic neuralgia, and 4.0 (3.6–5.4) in combined etiologies of peripheral neuropathy pain.[44] Gabapentanoids should be trialed for four to six weeks with two weeks at the maximum tolerated dose.[45] Effects are typically not seen in practice for three to four weeks.

The most commonly used anti-depressants for the treatment of chronic pain today are serotonin and norepinephrine reuptake inhibitors, such as duloxetine and venlafaxine. They facilitate descending inhibition by blocking serotonin and noradrenaline reuptake and have been shown to be effective in peripheral diabetic neuropathy, painful peripheral neuropathy, and

TABLE 36.3 Therapeutic Considerations

Neuropathic Pain		
	First line	• Gabapentinoids • SNRI anti-depressants • Caution with TCA • Carbamazepine and Oxcarbazepine in specific indications
	Second line	• Combination therapy • Tramadol • Tapentadol • Topical Lidocaine • Topical Capsaicin
	Third line	• Botulinum toxin A • Spinal cord stimulation • Intrathecal drug therapy
Nociceptive pain		
	First line	• Non-pharmacologic interventions • NSAIDs
	Second line	• Spinal cord stimulation
Spasticity related pain		
	First line	• Baclofen • Diazepam • Gabapentin • Tizanidine
	Second line	• Botulinum toxin A • Intrathecal drug therapy
Headaches		
	Acute measures	• Triptans
	Preventive measures	• Dihydroergotamine • CGRP inhibitors • Non-pharmacologic interventions

multiple sclerosis.[44,46] The NNT for 50% degree of pain relief in peripheral neuropathy is 5.1 (3.9–7.4).[44] The period of the trial should be limited to four to six weeks. Patients with comorbid depression may benefit from duloxetine, which can be used to treat both depression and neuropathic pain with similar higher dosing.[4,43]

TCAs, such as amitriptyline, nortriptyline, and desipramine, are less commonly used today because of their side effects. TCAs have multiple modes of action, with the most important pain-relieving effect likely due to the inhibition of serotonin and noradrenaline reuptake.[43,45] However, they also block histamine, adrenalin, acetylcholine, and sodium channels, accounting for their broad side effect profile. Their pain-relieving effect occurs in 20%–30% of the effective anti-depressant dose. Caution is required in the use of TCAs in the elderly and frail to avoid potential adverse effects, such as falls, cardiac arrhythmias, orthostasis, urinary retention, and dry mouth.[42] Based on a meta-analysis of randomized controlled trials, the NNT to obtain one patient with a 50% degree of pain relief is 2.8 (2.2–3.8) for painful polyneuropathy, 2.3 (2.1–2.7) for postherpetic neuralgia, 2.5 (1.4–11) for peripheral nerve injury, and 2.3 (2.1–2.7) for combined etiologies of peripheral neuropathy pain.[44] When trialing TCAs, it is recommended that it be done over four to eight weeks.[42]

Second Line Agents

Combination therapy is acknowledged as a significant part of the management. The combination of anti-depressants and pregabalin has shown efficacy in diabetic neuropathy. Combination therapy should be trialed for several weeks (determined by the specific added drug) and ceased if ineffective or if there are significant side effects.[47] Topical agents may also be employed.

Topical lidocaine works by decreasing ectopic firing of peripheral nerves, and both topical application and patch have shown efficacy for postherpetic neuralgia and mixed neuropathic pain with an NNT of 50% pain relief of 4.4 (2.5–17).[48] Topical lidocaine has been shown to be less effective in postsurgical neuropathic pain and diabetic peripheral neuropathy with allodynia or hyperalgesia.[44] The main advantage is the lack of significant side effects and safety profile in the elderly compared to the previous options.[47] Capsaicin is another topical choice. It binds to the TRPV1 receptor located on the Aδ and C-nerve fibers and results in the release of substance P and depolarization of the nerve.[42] Capsaicin has an NNT of 30%–50% pain relief of 11 (5.5–317) for painful polyneuropathy, 10–12 for postherpetic neuropathy, 6.5 (3.4–69) for peripheral nerve injury, and 11 for HIV-related peripheral neuropathy.[44] Despite their analgesic effect, the use of opioids is controversial, and they should be used as an adjunct second or third therapy, if at all. Several reviews have shown no evidence for using hydromorphone, fentanyl, morphine, or buprenorphine.[4,47,49,50] Combination therapy with gabapentin and opioids may provide better pain relief than gabapentin or opioids alone but is associated with higher rates of side effects.[47]

Tramadol has been shown to be effective in the treatment of painful polyneuropathy with an NNT of 3.5 (2.4–6.4) and in the treatment of postherpetic neuropathy with an NNT of 4.8 (2.6–27), with a combined etiologies NNT of 3.9 (2.7–6.7).[48,50,51] Tapentadol is a newer weak μ-receptor agonist and norepinephrine reuptake inhibitor. Its mechanism of action is slightly different from that of tramadol, with stronger noradrenaline reuptake inhibition and nearly no effect on serotonin reuptake. It is the first opioid that is FDA-approved for painful diabetic peripheral neuropathy. However, tapentadol efficacy remains inconclusive.[48] Anti-convulsants, such as lamotrigine, carbamazepine, topiramate, and sodium valproate, and N-Methyl-D-aspartate antagonists have been suggested. Nevertheless, no clear benefit was demonstrated, with a relatively higher number of side effects.[42]

Third Line Agents

More invasive options have been considered, including botulinum toxin type A, a neurotoxin that treats focal muscle hyperactivity with repeated administration locally over six months. Several small trials have studied its use in patients with postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy and showed an NNT of 1.9.[52] Neurostimulation is another treatment option. Patients should have a successful trial of stimulation (>50% pain relief) before permanent implant,[53] which is difficult to treat with SCS. Dorsal root ganglion stimulation and intrathecal drug therapy (IDT) have shown higher efficacy.[54] IDT involves the delivery of medications directly to their site of action at the dorsal horn of the spinal cord, bypassing the first pass effect and the blood–brain

barrier. This significantly increases the potency of the medication, allowing much smaller doses to be used. For effective therapy, patient selection is crucial and should undergo a successful trial before implantation.

Pain Associated With Spinal Cord Disorders

The differential diagnosis of spinal cord disorders that result in pain can be divided into infectious, demyelinating, vascular, trauma, and neoplastic etiologies. The evaluation includes specific history, physical/neurologic examination, and MRI imaging in most cases. The causes and locations of spinal cord disorders typically determine the need for surgical or medical management of the primary condition. Pain may be a prominent element in the manifestation of certain spinal cord disorders (e.g. spinal cord injury) or may occur as a late effect of the disease or therapy (e.g. radiation treatment or tumor resection). The characteristics of the pain experience, variable findings, and secondary pain generators are common to all spinal cord disorders.

The Workup

To differentiate between the different types of spinal cord disorders, specific history should assess the speed of symptom onset (acute or chronic), disease course (monophasic, relapsing, progressive, complete or partial), additional clinical features (pain, visual symptoms in multiple sclerosis (MS), systemic symptoms in autoimmune disorders, and lung/eye/skin involvement in sarcoidosis. MRI can distinguish between lesions according to position, size, and enhancing pattern.[55]

Hyperacute onset (minutes to hours) includes vascular etiologies (spinal infarction and/or, more rarely, hemorrhage). Infarction phenotypes are classified according to the vascular supply involved. The most frequently encountered clinical presentation is symmetric motor dysfunction, bilateral spinothalamic sensory deficit below the level of the lesion, autonomic sphincter dysfunction, and flaccid weakness associated with areflexia. Weakness is due to anterior and lateral column dysfunction as a result of anterior spinal artery territory infarction. Posterior spinal artery infarcts are rare and involve proprioception and vibration loss below the level of the injury besides complete anesthesia at the level of the lesion.[56]

Acute/subacute onset (days to weeks) can suggest trauma, infectious, inflammatory, autoimmune, demyelinating, neoplastic, paraneoplastic, and metabolic etiologies.

Etiologies of chronic onset (months to years) may include infectious, neoplastic, paraneoplastic, autoimmune, metabolic, and vascular causes.[55] Tumors comprise a small percentage of cases. Here, the pain that slowly starts initially fluctuates prior to becoming more constant, gradually increases and worsens at night when the patient is recumbent, and eventually disturbs the patient even at rest and is considered the most typical sign for spinal tumors.

Additional information should include medical, surgical, family, and detailed social histories. If a suspected infectious etiology occurs, patients should be further asked about any recent infection, an immunocompromised or autoimmune condition, space-occupying lesion, travel, vaccination, trauma, sexual exposure, and/or animal/insect bites. The assessment of pain as the chief complaint begins with medical history concerning pain descriptors, including pain onset, time course, pain location, intensity, quality, quantity, alleviating and aggravating factors, clonus and/or spasticity, medications, and medications, previous evaluations, and treatments. Associated cord symptoms, including bladder and bowel control, weakness, and altered sensations, should be investigated. Functional capacity history, including both occupational and recreational history, should be obtained for functional impact as well as possible pain promoters (such as wheelchair, crutch, or cane use).[57] Psychosocial comorbidity assessment is required to assess depression, anxiety, personality disorders, substance use, personality disorders, and cognitive deficits.[58]

Physical examination should be broadly systemic and should focus on neurologic findings such as motor weakness, changes in sensation such as allodynia, hyperalgesia, and hyperpathia (pinprick, light touch, vibration, position sense, or temperature), tone, muscle stretch reflexes, coordination, muscle overactivity (clonus, spasticity, spasms), focal examination of specific pain regions, and bowel and bladder function. Local back tenderness may suggest trauma, osteoporotic fractures, or a tumor. Gait (if possible), how the walking aids are used, and functional capacity should all be observed.

Following the history and physical examination, either computed tomography (CT) (in case of bony lesions) or MRI (preferred in most cases) is required for diagnosis.[59] Short lesions (<three segments) suggest MS, sarcoidosis, or neoplasm (primary or metastatic). Long lesions may be due to infections, metabolic, neoplasms, vascular lesions, and sarcoidosis.[55] In cases of suspected vascular lesions, MR angiography or digital subtraction angiography is needed. NCS and electromyography are rarely helpful in primary spinal cord disorders but may rule out peripheral disease. Laboratory tests can assist in the investigation of systemic pathologies, such as multiple myeloma, malignancy, and spondylarthritis. In cases of suspected spinal cord infarction, inflammatory or infectious etiologies should include CBC, chemistry, metals, vitamin B12, vitamin D, viral and bacterial serologies, Lyme titers, vasculitis markers, hypercoagulable profile, and paraneoplastic autoantibodies.[60] CSF analysis may be considered for bacterial and viral infections (pleocytosis), inflammation/autoimmune causes, suspected demyelination (oligoclonal bands), and/or suspected sarcoidosis (ACE). Tissue biopsy is infrequently performed. For malignant lesions with specific treatment implications, a biopsy is necessary to confirm the diagnosis and histologic type.[55]

Following specific spinal cord disorder diagnosis, classifying patients with pain according to a mechanism-based approach may help choose the most appropriate treatment. Evaluation is based on medical history, investigating complex pain features, spasticity, disability, and psychological factors. Pain may be related to bowel, bladder, or kidney dysfunction or distention but may also represent a neuropathic type of pain. Below-level pain has typical neuropathic descriptors, including shock-like, sharp, shooting, squeezing, and burning. It is distributed in more than three dermatomes below the neurologic level of injury but may extend up to the level of injury. Pain may be triggered by sudden noises, vibration or physical jarring, urinary tract infection, constipation, or skin problems (spinal cord injury-induced pain: mechanisms and treatments). At-level pain has typical neuropathic features, such as below-level pain. Above-level pain generators are heterogeneous, such as those of "ergonomic" pathology secondary to overuse of the shoulders and arms causing myofascial pain in the shoulder joints from wheelchair use, or "crutch palsy" resulting from mechanical compression of nerves from orthotics. It is usually a musculoskeletal type of pain and is described as dull and aching. Postural anomalies may worsen this situation. Often, accompanying central pain are symptoms associated with

autonomic dysreflexia, including increased or decreased blood pressure, pulse, and headache.

The Differential Diagnosis

Traumatic Spinal Cord Injury

Pain is a frequent consequence of both complete and incomplete spinal cord lesions.[61] A recent systematic review estimated the prevalence of any type of pain after spinal cord injury (SCI) at 61%.[62] Among all types of SCIs, below-level pain is the most common (23%–52%) and the most difficult to treat. It has a mean onset time of 1.8 years. At-level and above-level pain also occur a year after SCI.[63] Visceral pain occurs later (mean of 4.2 years).[63]

Syringomyelia most commonly follows trauma but may also be congenital (associated with Arnold-Chiari malformation), postinfectious (associated with arachnoiditis), or associated with intramedullary spinal cord tumors. Post-trauma, this diagnosis should be considered if there is a worsening of motor/sensory/autonomic issues and/or spasticity. Atrophy and fasciculations indicate the involvement of the anterior horn cell columns by the syrinx. Patients with a cervical syrinx will have pain and numbness typically in a "cape" distribution. Extension into the upper cervical region may be associated with ipsilateral facial pain caused by the involvement of the descending trigeminal tract and nucleus. Thoracic syringomyelia manifests as neuropathic pain in the trunk or abdominal distribution, dissociated distal sensory loss, spasticity, and urinary retention. Lower thoracic syringomyelia will exhibit symptoms of dysfunction of the conus medullaris, with prominent sacral neuropathic pain and urinary retention.

Demyelinating Disease

MS is a relapsing, remitting, and chronic progressive autoimmune disorder involving central nervous system demyelination. Acute exacerbations are associated with acute inflammation of the central myelin in the optic nerves, periventricular white matter, the brainstem, and the spinal cord. Diagnostic criteria include MRI evidence of damage in at least two separate locations in either the brain or spine and evidence of damage that occurred at different times (either clinically and/or MRI). The prevalence of pain ranges between 26% and 86%. Although neuropathic, MS pain is multifactorial and can have neuropathic and nociceptive origins and may be strongly associated with multiple psychological comorbidities.[64] With the increasing burden of disease, it is likely that the intensity, location, and complexity of the pain in MS progress, along with neurologic disorders. Pain has a significant impact on psychosocial functioning, daily activities, mood, and sleep.[65,66]

MS-associated neuropathic pain syndromes include dysesthetic extremity pain, Lhermitte's phenomenon, secondary trigeminal neuralgia, and optic neuritis. Dysesthetic extremity pain is characterized by constant burning pain in the legs and feet, with nocturnal exacerbations. Lhermitte's phenomenon is a short electric shock-like sensation felt in the back of the neck and lower back, occurring mainly with MS flares, is usually provoked by neck flexion, and is limited in clinical course to a 4- to 6-month period.[57] Spasms and headaches are common in these patients.[67] Box 36.1 summarizes the pain conditions associated with MS.

Infectious

Transverse Myelitis. Transverse myelitis (TM) is a focal inflammation of one or more levels across the spinal cord in the absence of a compressive lesion. This inflammation can cause damage to the myelin, resulting in pain and neurologic dysfunction, including weakness of the lower limbs or of all four limbs, sensory level impairments, and bowel and bladder problems. Different bacterial, viral, fungal, and parasitic infections can cause TM in addition to several autoimmune diseases (MS, neuromyelitis optica). Pain is a common symptom in 33%–50% of patients and may be central or localized, aching or radicular in character.[68] Diagnosis is confirmed with MRI, which allows visualization of the lesion and rules out treatable causes, such as a tumor, abscess, and other lesions causing compressive myelopathy.[69] Labs should include blood counts and chemistry, tests for autoimmune conditions, and Lyme/viral titers. Pleocytosis and oligoclonal bands in the CSF support the diagnosis.[68] NCS may be helpful for disease monitoring.

Tabes Dorsalis. Neurosyphilitic involvement of the dorsal root entry zone is a classic neurologic pain disorder. The disorder is characterized by "lightning pain" involving the lower extremities. Similar pain may occur in the trunk, thorax, and abdomen. Tabetic pain may occur for brief periods (seconds or minutes) or last for several days. Occasionally, visceral involvement predominates, known as "visceral crises." These crises are characterized by epigastric or pelvic pain, accompanied by nausea or vomiting. Physical examination is remarkable for the loss of sensory modalities distally in the lower extremities. There may also be significant ataxia, hypotonia, and dysautonomia. CSF analysis demonstrating positive venereal disease research laboratory test (VDRL) or fluorescent treponemal antibody absorption (FTA-ABS) is diagnostic. The classic finding of Charcot's joints results from deep anesthesia caused by the disorder.

Osteomyelitis. Osteomyelitis may develop after trauma to the spine, postsurgery, or via hematogenous spread from an adjacent site. It is most often a single pathogen infection, and *Staphylococcus aureus* is the most common pathogen.[60] Back pain is the most common presenting symptom, with fever being present in only 35%–60% of cases. The most common site was the lumbar spine (58%), followed by the thoracic spine (30%) and cervical spine (11%). Physical examination may detect spine tenderness and neurologic deficits, including sensory loss, weakness, or radiculopathy, in 33% of cases.[60] Laboratory tests, including CBC, ESR, CRP, and blood cultures, may be used.[70] MRI is the modality of choice for diagnosis, demonstrating signal changes in the vertebral endplates, disc space, and epidural hematoma. Percutaneous aspiration or biopsy can isolate microorganisms when blood cultures are negative.[70]

• Box 36.1 Pain Conditions Associated With Multiple Sclerosis

Neuropathic Pain

Acute transverse myelitis
Acute radicular pain
Chronic myelopathy (deafferentation pain, transitional pain, radicular pain)
Focal peripheral neuropathies (secondary to disability)

Myofascial Pain

Spasticity secondary to myelopathy
Regional myofascial pain (overuse syndromes, posture and gait disorders)
Diffuse myofascial pain (chronic fatigue, sleep deprivation)

Musculoskeletal Pain

Overuse syndromes (wheelchair-bound patients)
Accelerated osteoporosis because of immobility

Vascular

Spinal cord infarction is relatively uncommon, estimated at 1%–2% of ischemic strokes, due to the extensive collateral vascular network. The risk of spinal cord stroke increases significantly during thoracoabdominal aortic surgery. Symptoms are usually abrupt in onset and progress rapidly from minutes to hours. Over 70% of spinal stroke patients suffer from back and/or limb pain.[71] Suspected patients are managed with hemodynamic support to maximize blood pressure and sometimes lumbar drainage to lower CSF pressure.[72] A long-term follow-up study found that spinal patients had higher rates of employment and lower mortality than cerebral stroke patients but higher rates of chronic pain and lower functional independence (modified Rankin scale).[71] The main component of pain is neuropathic and can be treated with neuromodulatory drugs.[73]

Spinal vascular malformations are another relevant vascular pathology that may include cavernomas, intradural arteriovenous malformations (AVM), dural arteriovenous fistulas (AVF), and perimedullary AVFs.[74] Presentation can range from an incidental radiologic finding, a slow-progressing myelopathy or polyradiculopathy (cavernomas, perimedullary AVF), and ischemic injury (dural AVF), which results in progressive myelopathy, subarachnoid hemorrhage with sharp back pain, and catastrophic neurologic injury (intradural AVM, perimedullary AVF).[74]

Typical patients are often younger.[74] Physical examination may be normal or detect different stages of myelopathy. Skin examination for cutaneous angiomata and examination of the extremities for limb hypertrophy may suggest genetic syndromes. MR angiography (CT angiography when MR is not available or contraindicated) or digital subtraction angiography is invaluable. Following hemorrhage or progressive neurologic deficit, most symptomatic malformations are treated either by surgery, radiosurgery, or endovascular intervention for complete or partial excision or embolization of the lesion. Chronic pain is one of the predominant symptoms induced by spinal AVMs or hemorrhage.[75] It has been reported to persist in up to 80% of cases post-treatment, significantly affecting patients' quality of life.[76] Neuropathic pain can be treated with medications. However, it is frequently refractory to pharmacologic modalities.

Tumor

Spinal tumors can be classified into three groups based on their location: extradural, intradural extramedullary, and intramedullary. Extradural tumors are the most common, as they occupy the vertebral body or structures outside the dura. They are the most commonly metastatic. Intradural extramedullary tumors are characterized by meningiomas or neurofibromas. The least common (2% to 5%) is intramedullary spinal cord tumors that arise from the spinal cord, leading to invasion and destruction of the gray and white matter. Ependymomas and astrocytomas are the most common intramedullary spinal cord tumors, followed by hemangioblastomas. Pain is the most common presenting symptom, and its distribution depends on tumor location. In addition, motor weakness, sensory changes, ataxia, and loss of bladder/bowel function can occur.[77] In patients with suspected spine tumors, CT can assist in extradural lesions and bony lesions, including fractures, osteolytic metastasis, and osteoblastic metastasis (prostate and breast). MRI is the preferred modality to characterize the lesion, size, location, length, extent of the surrounding edema, presence of the cord-tumor interface, and associated cysts or syringomyelia.[77]

Treatment

The first step includes specific treatments per etiology. Traumatic SCI and spinal infarction should be managed acutely with hemodynamic stabilization and prevention of secondary injury. Surgical intervention is indicated in cases of instability or spinal cord or nerve compression. Vascular lesions can be treated surgically or via endovascular intervention. MS should be treated with specific disease-modulating drugs.

For infectious etiologies, surgery for an epidural abscess in the face of neurologic deficit and long-term antibiotic treatments may be needed. TM treatment involves anti-inflammatory treatments, including corticosteroids, immunosuppressive agents, IVIG, and plasma exchange, along with intensive physical therapy and rehabilitation programs. Braces are used to provide stability and reduce pain in ambulation.[78] To treat syringomyelia, neurosurgical drainage of the syrinx, surgical resection of a spinal cord tumor (when present), or both can help ease symptoms. Syrinx drainage is primarily performed to limit neurologic progression. However, alleviation of central pain following drainage of the syrinx is not uncommon.[79]

In cases of extradural metastasis, spinal instability, vertebral collapse with or without any neurologic deficit, radiotherapy-resistant tumors, intolerable pain unresponsive to conventional therapy, and neurologic deficits before, during, or after radiotherapy are indications for surgery. Surgery is the best treatment option for pain and neurologic symptoms caused by spinal instability. Surgical resection should be performed as soon as possible following a diagnosis of intradural tumor, as outcomes correlate with the preoperative neurologic conditions, and observation can lead to further neurologic deficits, some of which are irreversible. Postoperative radiotherapy may be indicated, depending on the pathology.[80] Vertebroplasty and kyphoplasty may be considered for selected pathologic fractures.[81] Following the primary intervention, all factors involved in producing the associated residual pain must be identified and addressed separately. The realistic goal is to reduce the intensity of the pain to a tolerable level with interventions that have acceptable risks and costs.

Medical Management

Physiotherapy with targeted exercise programs can alleviate pain and spasticity. A regular exercise regimen or yoga may be beneficial for alleviating diffuse nociceptive pain symptoms. In addition, occupational therapy can address biomechanical abnormalities associated with mobility aids. Modification of orthotics, canes, walkers, crutches, and wheelchairs can potentially influence detrimental ergonomics. Concomitant sleep disorders and depression should be addressed and treated by non-pharmacologic means (e.g. sleep hygiene measures, cognitive behavior therapy [CBT] if required) and pharmacologic modalities when appropriate.

First line therapies for at-level and below-level neuropathic pain include gabapentinoids (pregabalin and gabapentin) with a combined NNT of 6.3–8.3 (for all neuropathic pain) and antidepressants.[48] Second line therapies include tramadol and anticonvulsant lamotrigine, which is a voltage-sensitive sodium channel inhibitor. Other sodium channel blockers, carbamazepine, and oxcarbazepine have been suggested for paroxysmal pain and Lhermitte's in MS.[82] Third line therapies in selected patients include combination therapy.

Intractable neuropathic pain may be treated with IDT.[83] Patients with impaired sensation after SCI are much less responsive to tonic

SCS than others. The efficacy of new SCS paradigms with paresthesia-free SCS for SCI pain requires further investigation.[78] SCS may benefit MS-related symptoms as shown in one study with follow up of 97 months, wherein 74.1% of patients retained significant pain improvement after implantation.[84]

Multiple non-drug related treatment strategies, including transcranial direct current stimulation, rTMS, cranial electrotherapy stimulation, acupuncture, self-hypnosis, TENS, and CBT, are not well established.[85]

Spasticity Related Pain

Muscle stretching is a common practice in the management of spasticity and related pain to reduce muscle tone, maintain or increase soft tissue extensibility, reduce pain, and improve function, but the available evidence on its efficacy is inconclusive. Spasticity can also be addressed with antispasticity medications, such as baclofen, diazepam, gabapentin, and tizanidine. Botulinum toxin A injections can be added to treat focal spasticity (adductors). Sodium channel blockers (carbamazepine and oxcarbazepine) have been suggested as the first line treatment for painful spasms.[86] Cannabinoids and gabapentin have been shown to have an antispasticity effect leading to improvement in spasticity related pain.

The use of intrathecal baclofen (ITB) for diffuse spasticity is recognized as an effective therapy for patients with an incomplete response to oral therapy. In non-ambulatory MS patients, ITB has been shown to provide relief of discomfort and pain related to spasticity, greater ease of care, improved posture, and improved ability to transfer.[84] Repeated MRIs remain possible.[87] Primary surgery is usually considered for selected patients with contractures. The goals of surgical treatment include improvement of function and autonomy, control of pain, and prevention of orthopedic disorders (Table 36.3).[88]

Central Pain Syndromes Due to Brain Pathology

Lesions in the brain may lead to chronic central pain. Etiologies can be divided into degenerative, demyelinated, traumatic, neoplastic, and vascular. Central pain presentation depends chiefly on the site of the lesion, not on the size of the lesion or the specific pathology. The neuroanatomic substrate for brain central neuropathic pain involves a lesion along the somatosensory pathways in the brainstem trigeminothalamic pathways, medial lemniscus, thalamus, thalamocortical projections, and somatosensory cerebral cortex.

The Workup

Differentiation between different brain pathologies requires a specific history, neurologic examination, brain imaging (preferably MRI), and specific tests per suspected diagnosis. History should assess the time course of onset (days, weeks, years) and progression of different symptoms (constant, attacks, progressive) and distribution of symptoms (hemibody/bilaterally, involving one or more limbs, involving the trunk, involving the face and head). Symptoms may include pain, facial and/or sensory body changes, facial and/or body motor weakness, visual deficits, speech difficulties, muscle spasms, spasticity, and bladder and bowel symptoms. Pain descriptors, including location, timing, intensity, quality, and alleviating and aggravating factors, should be explored. History should also include details of previous ischemic/hemorrhagic event/brain trauma, previous therapeutic interventions, previous and current functioning, social history, family history (including dementia, movement disorders, cancer, cardiovascular and psychiatric diseases), and psychological comorbidities including depression and anxiety.

Complete neurologic examination should be performed, including observation of facial expression, examination of cranial nerves, muscle power and tone, tendon and pathologic reflexes, sensory evaluation, gait, and function. Orientation, reasoning, and short memory are assessed when cognitive decline is suspected. Rigidity, muscular spasticity, paresis-related malposition, overuse, contractures, and decubitus ulcers should be carefully examined as other non-central pain generators. Brain MRI is required for lesion definition and ruling out secondary abnormalities (such as hydrocephalus post-stroke/trauma, new MS plaque) and the correspondence with current symptoms. In addition to anatomic sequences, in cases of suspected vascular lesions or trigeminal neuralgia, specific sequences and/or angiography (CT or MR based) may be required to visualize the cerebral blood vessels properly.

Differential Diagnosis

Vascular Etiology

The classic and most characteristic central neuropathic pain condition is central post-stroke pain, accounting for approximately 90% of central pain syndromes.[89] It is estimated to occur in approximately 10% of individuals after the first year following a stroke. The lesion may be in the thalamus (most common), medulla, spinothalamic tracts, operculum, or insular cortex and can cause chronic pain.[90] Post-stroke pain typically coexists with a concomitant contralateral sensory deficit. Pain most commonly begins one to three months after stroke, with most affected patients developing symptoms by six months.[91] Remarkably, there may be a very mild motor deficit compared to significant pain and hemi hypoesthesia.

Patients with brainstem infarctions, particularly lateral medullary infarcts (Wallenberg syndrome), may also be affected by central neuropathic pain. Ipsilateral neuropathic facial pain may coexist with contralateral sensory deficits.[92] Evaluation includes a history of ischemic/hemorrhagic events, previous functioning, and pain descriptors. In addition to neurologic examination and assessment of deficits, physical examination is important to rule out other pain generators. Other pains need to be distinguished from central pain, including spasticity, paresis-related malposition, overuse of the unaffected body site, painful shoulder-arm syndrome after subluxation of the scapulohumeral joint, or CRPS of the paretic arm that developed due to a peripheral trauma secondary to the stroke.[89] Brain imaging should be considered for evaluation of secondary lesions post-stroke.

Trigeminal Neuralgia

Severe pain is characterized by recurrent unilateral orofacial pain that is restricted to one or more branches of the trigeminal nerve. The incidence of trigeminal neuralgia (TN) is estimated to be 12 per 100,000 per year.[93] Pain is usually described as shooting, electric, shock-like, stabbing, or sharp attacks lasting several seconds to a few minutes. Facial movements classically trigger attacks during talking, eating, or mechanical stimulation, such as shaving. TN is classified as idiopathic TN, trigeminal neuropathic pain (unintentional injury), trigeminal deafferentation pain (intentional injury), symptomatic TN (associated with MS), postherpetic TN, and atypical facial pain (which is not considered TN). Idiopathic

TN is further divided into TN1 and TN2. TN1 is defined by the symptomatic description of a sharp, shooting electric shock-like episodic pain, whereas TN2 is described as aching, throbbing, and burning pain, which is constant over 50% of the time. Both TN types 1 and 2 may occur due to compression of the trigeminal nerve root entry zone. In cases of facial pain with the features of TN2, the likelihood of detecting a structural entity, such as a tumor or vascular malformation in the posterior fossa is higher.[94]

The diagnosis is based on typical pain descriptors and location, along with ruling out of other headache and facial pain generators, including oral cavity and salivary gland lesions, paranasal sinus disease, cluster headaches, and other types of trigeminal neuropathy.

Classic pain triggers include mastication, touch, tooth brushing, eating, talking, and cold winds on the face. Neurologic examination should rule out cranial nerve deficits that are usually absent in idiopathic TN. Next, brain MRI should follow to locate a possible trigeminal nerve compression by a blood vessel and rule out posterior fossa lesions such as tumors, stroke or MS plaque, and other causes of facial pain.[95] Treatment usually includes pharmacologic therapy with sodium channel blockers (carbamazepine, oxcarbazepine, or gabapentin). Botulinum toxin A injections[93] can also be used. However, refractory pain mandates different surgical interventions, including microvascular decompression, radiosurgery, and three types of trigeminal nerve rhizotomies (balloon compression, glycerol rhizotomy, and radiofrequency rhizotomy). The TN is discussed in Chapter 38.

Degenerative Disease

Parkinson's disease. Parkinson's disease (PD) is a slowly progressive movement disorder characterized by resting tremor, rigidity, and bradykinesia. It typically occurs in older individuals with variable progression patterns. With progression of the disease, patients typically have significant motor fluctuations with "on" periods of relative ease of movement interspersed with "off" periods of rigidity, bradykinesia, and tremor. Between 40% and 85% of patients with PD have chronic pain that frequently includes more than one type of pain.[96] The different pain subtypes associated with PD can be classified as musculoskeletal pain (most frequent), articular/arthritic pain, neuropathic pain, radicular pain, pain due to dystonia, pain due to rigor/bradykinesia, akathitic discomfort, restless legs syndrome, and central pain.[97] More than 50% of the patients report one type of pain, 24% report two, and 5% report three pain types. Of these, musculoskeletal pain was noted in 70%, dystonic pain in 40%, radicular-neuropathic pain in 20%, and central neuropathic pain in 10%.[98] Pain in PD correlates with age, disease duration, and severity, and, as with many pain conditions, female sex is a significant predictor of pain.[99]

Pain assessment in PD involves obtaining a careful history of whether the patients are appropriately medicated from a dopaminergic standpoint. A neurologic examination can help determine the relationship between the symptoms and medication dosing. That is, if pain occurs when medications are worn off, additional dopamine may be needed. Restless leg syndrome should be treated with low-dose dopamine agonists before nighttime. Botulinum toxin A can be used to treat dystonia-associated pain. Abdominal pain secondary to constipation can be treated using macrogol. Neuromodulatory medications may also be useful. Subthalamic nuclei and globus pallidal deep brain stimulation (DBS) performed mainly for motor symptom control have shown significant long-lasting pain relief effects in selected patients.[100–102]

Dystonia may occur outside the PD as an isolated disorder. It may be either primary or secondary. Primary dystonia is hereditary. Secondary dystonia is post-infectious, posttraumatic (usually following peripheral nerve trauma), and/or idiopathic forms. Dystonias are classified according to the extent of neuromuscular involvement: focal, segmental, multifocal, or generalized. There may be profound contractures that are painful. Dystonia-related pain treatment (including PD) includes dopaminergic agents, anticholinergic agents, muscle relaxants (e.g. baclofen), and benzodiazepines. In focal dystonias, especially idiopathic cervical dystonia, the use of locally injected botulinum toxin has resulted in significant symptomatic benefit and is the first line therapy.[103]

Alzheimer's Disease. Alzheimer's disease (AD) is a neurodegenerative disorder and the most common form of dementia. History should be obtained from both the patient and a close family member or friend. History should characterize the nature (language, word-finding, episodic memory), magnitude (severity and daily life function), and course of cognitive changes (speed of onset and pattern of progression). History should include comorbidities (hypertension, previous brain injury, or stroke), medications that may impair cognition (e.g. benzodiazepines), and family history (especially dementia). Neurologic examination should evaluate frontal disinhibition (hyperorality, hypersexuality), unusual behaviors, parkinsonism, or other focal neurologic signs. Cognitive assessment should be conducted using a screening tool (such as the Montreal cognitive assessment).[104] Formal neuropsychological evaluation should follow. The laboratory panel should include CBC, renal and liver function, thyroid function, and B12 and B1 levels. Brain imaging should be performed to rule out other etiologies and evaluate general atrophy and hippocampal atrophy.[105]

The reported prevalence of chronic pain in AD patients is 45.8%, based on a recent meta-analysis.[106] Pain processing may be altered in patients with dementia. Due to patients' diminished ability to report pain and/or side effects in connection with the pain treatment, pain evaluation/treatment is even more complex. The prevalence of undiagnosed and untreated pain is described as unacceptably high in the primary healthcare system, with a reported prevalence of up to 32% in home-dwelling people with dementia and about 60% in nursing home patients.[107] Development of a comprehensive treatment plan is essential in the population with dementia. Using an interdisciplinary approach is key to establishing a multimodal pain management plan.[108] The incorporation of non-pharmacologic interventions, including exercise and/or movement therapies, psychological interventions, massage, heat and relaxation therapies, and human interactions, has a significant effect on chronic pain.[109]

When pain cannot be relieved by either targeting the cause of pain and/or applying non-pharmacologic strategies alone, pharmacologic treatment of pain is necessary with neuromodulatory medications for neuropathic pain and nonsteroidal analgesics (nonsteroidal anti-inflammatory drugs) for nociceptive pain.

Demyelinating Disease

As noted earlier, MS is a relapsing, remitting, and chronic progressive disorder. Pain in MS may also result from brain lesions. Most commonly, this may include headaches (35%–61%), dysesthetic pain (18.1%), and TN (2%)[110] (see Box 36.1). The diagnosis of TN can precede the diagnosis of MS in up to 15% of the patients.[110]

Evaluation should include a history of the disease and headaches description including quality, intensity, location, timing, and associated aura and symptoms. Neurologic examination should assess the current status and rule out new deficits. MS patients can suffer from different types of headaches, including migraines, tension in addition to cranial neuralgias (trigeminal, occipital, and glossopharyngeal neuralgias), and disease-modifying drug related headaches (interferon-β, natalizumab, and others).[111] Depression, anxiety, and other psychiatric disorders, when combined with life stressors, have a negative impact on headaches.[112] Interventions that include anti-depressants and CBT have a favorable outcome.[113]

Trauma

Besides cognitive changes that occur in traumatic brain injury (TBI), motor deficits, and sensory abnormalities, accumulating evidence suggests that acute and chronic pain are also common after TBI. Chronic pain occurs in 43.8%–45.5% of these patients.[114] A recent analysis concluded that mild TBI was associated with a 75.3% rate of pain, while moderate to severe TBI was associated with a 32.1% rate of pain.[115] Chronic pain can occur independently of concomitant diagnoses of depression and post-traumatic stress disorder.[116] Naturally, headaches are the most common type of pain,[116] followed by neck, shoulder, back, and upper and lower limb pain. Some TBI patients develop a late-onset pain syndrome, six months or more after injury, with characteristics similar to post-stroke chronic pain.[117] Severe symptoms following severe TBI mandate either CT or MRI imaging to rule out posttraumatic complications, such as hydrocephalus, hemorrhages, strokes, and skull defects related and others.

Posttraumatic headaches may be similar to other types of headaches. Patients may also experience debilitating headache exacerbations in the absence of aggravating factors, resembling a state of dysesthesia commonly found in other neuropathic pain states.[118] The sensory profiles of patients with posttraumatic headaches have higher thermal thresholds and lower mechanical pain thresholds in the hands and face, suggestive of a central origin of pain.[118] Their scalps are often very sensitive to light touch. Early identification and intervention are key factors in the management of pain conditions and emotional distress related to TBI, both in the acute and chronic stages. Moreover, severe initial pain intensity has been identified as a risk factor for developing chronic pain post-TBI, which may be prevented if treated early.[119]

Comorbid cognitive impairments, including attentional and memory problems, should be assessed. Comorbid mood dysfunction, such as major depression or anxiety and suicidality, should be documented.

The Treatment

Initially, each central pain syndrome requires primary treatment for the disease. MS-specific drugs are prescribed or changed to reduce the frequency of attacks and/or disease progression. Neuromodulatory medications are used for TN, post-stroke pain, and post-TBI pain. Patients with PD and dystonia must be medically optimized.

In conjunction, neuromodulatory medications may be used, including those discussed above, for spinal and peripheral nerve pathology. TN medical management differs slightly as it begins with carbamazepine. Restless leg syndrome should be treated with low-dose dopamine agonists before nighttime, whereas gabapentin and pregabalin are second line therapies.

Several neuromodulation treatments have shown efficacy in cases of refractory pain, intolerance, or resistance to pharmacologic therapy. DBS has been shown to relieve central pain to various degrees, sometimes even allowing for complete discontinuation of pain medications. Meta-analysis of DBS implanted in the ventral posterolateral thalamus nuclei and periventricular/periaqueductal gray matter has shown that over 50%–80% of patients who underwent a stimulation trial elected a permanent device surgery with over 50% showing long-term pain relief.[120,121] Motor cortex stimulation (MCS), involving the implementation of electrodes epidurally over the motor cortex, has shown significant visual analog scale reduction in several cases in a series of patients with post-stroke pain.[122] In addition, MCS has shown promising results in chronic refractory cases; 72%–84% of trialed subjects pursue permanent implantation of the system, and over 80% of them have good pain control.[123]

With motor weakness, other pain can occur due to immobility of the hemiplegic limbs or contractures. Occupational therapy, physical therapy, stretching, or bracing may be used. Botulinum toxin A and ITB may be used for medical management failure. Functional electrical stimulation may serve as an adjunct.[124,125] Secondary pain complaints may be proactively managed by symptomatic treatment of arthralgia, management of concomitant osteoarthritis, and prevention of falls.

In patients with headaches, management depends on the type of headache. Migraine management includes triptans, which act as selective activators of the 5-HT receptors, dihydroergotamine, which is an agonist of serotonin and other receptors, and calcitonin gene-related peptide (CGRP) inhibitors.[119,126] Topiramate and erenumab, a CGRP inhibitor, have shown some efficacy in posttraumatic headaches.[127,128] Although behavioral therapeutic modalities, such as CBT, biofeedback, and relaxation, are well accepted for primary headache prevention, their applications and efficacy for posttraumatic headaches are unknown.[129] Regular aerobic exercise can improve post-concussion and MS symptoms and should be encouraged; patients should be informed that it does not cause symptom exacerbation and that this is an important method to improve post-concussion symptoms.[130]

Conclusion

Pain is a frequent component of a wide spectrum of neurologic disorders that results from a wide range of pathophysiologies. Following the diagnosis and management of the disease, evaluation should focus on identifying all factors and different types of pain generators. Therapy should be tailored for each type of pain in a stepwise manner, considering baseline disease and comorbidities.

Key Points

- Disorders of the peripheral nerves, spinal cord, and brain may result in chronic pain.
- Peripheral neuropathy evaluation includes history, examination, stepwise labs, and EMG. A skin biopsy may be indicated for small fiber neuropathies.
- Brain and spine disorder evaluation includes history, physical examination, laboratory tests, and MRI.
- The primary goal of pain evaluation in neurologic patients is the discernment of the type of the most disabling pain, its origin, and classification (neuropathic, nociceptive, visceral spasticity related). Most patients have more than one type of pain generator.
- Following primary disease management, therapy should be tailored to address each type of pain using a stepwise approach, including pharmacologic, non-pharmacologic, and neuromodulation interventions.
- Neuropathic pain is mainly treated with medications, including gabapentinoids and SNRIs. Neuromodulation (SCS, DRG) or intrathecal drug delivery can provide relief in refractory cases.
- Spasticity is a major source of myofascial pain in central disorders and is primarily treated with muscle relaxants or intrathecal drug delivery. Botulinum toxin A injections can be used to treat focal spasticity.
- All chronic pain is biopsychosocial, and it is critical to embrace psychosocial dysfunction pain because these features are often easier to treat than biomedical targets.

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Chronic Widespread Pain

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Chronic widespread pain presents challenges to patients, clinicians, and researchers in diagnosing and treating its complex manifestations. Chronic widespread pain is a broad category of heterogeneous, centrally mediated pain conditions. While recent advances in understanding centrally mediated pain have improved its mechanistic understanding, consistently applying clinical diagnosis and treatment remains challenging. The unifying theme for these disorders is pain and sensory hyper-responsiveness, which can be identified using sensory testing and is associated with functional neuroimaging changes.[1] Although widespread pain conditions, including fibromyalgia (FM) conditions, have historically struggled for credibility, advances in our mechanistic understanding of these conditions have occurred so rapidly that we can now use this information to better diagnose and treat individuals with chronic pain. FM is a painful condition for a third new descriptor of pain, nociplastic pain, which has been recently adopted by the International Association for the Study of Pain.[2]

Longstanding negative perceptions and beliefs about centrally mediated pain states are likely to interfere with the adoption of standardized treatment protocols. However, some of the objective tests that can be used to identify pathology in these conditions, such as quantitative sensory testing and functional neuroimaging, are not generally available clinically. Despite this, clinicians can use various simple patient-reported outcomes to make inferences regarding underlying pain mechanisms. This chapter summarizes the current status of these chronic widespread pain conditions, focusing on fibromyalgia and its clinical features, epidemiology, pathogenesis, and management.

Fibromyalgia

Evolution of Diagnostic Criteria

One of the more recent developments in understanding fibromyalgia (FM) has been the paradigm shift in evaluating fibromyalgia as a continuum rather than a binary diagnosis. However, the move toward clinical diagnostic criteria and the use of tools such as the current 2011 FM survey criteria have taken a lengthy path to reach our current state. The first American College of Rheumatology (ACR) developed research criteria for the classification of FM syndrome based on the results of a multicenter research study in 1990 (Table 37.1). The scientific community quickly accepted these criteria with a broad application for epidemiologic, biologic, and therapeutic studies. The ACR research classification required only two components for diagnosis: a history of widespread pain (i.e. located in all four quadrants of the body and axial) for at least three months and allodynia in response to digital pressure (defined as pain with 4 kg of pressure) at 11 or more of the 18 anatomically defined tender points (Table 37.2). The research diagnostic criteria demonstrated moderate sensitivity (88.4%) and specificity (81.1%) for FM in control patients. The study design included pain-free individuals and patients with other painful conditions as the control group.

The tender points in FM are conceptually and anatomically different from the trigger points (TrPs) that define myofascial pain syndrome (MPS). FM tender points are symmetrically distributed throughout the body, whereas TrPs have a more random distribution. In contrast to MPS, these tender points are not limited to muscular locations but also include other soft tissue structures and do not radiate or refer pain to other locations.

The ACR's original research criteria provided a structure but did not extend to clinical applications. Researchers have developed these criteria to standardize the research identification of FM. The research classification identified 18 anatomically defined tender points (Table 37.2), where patients with FM have allodynia in response to digital pressure. Lacking alternative algorithms for diagnosis, clinicians have appropriated these criteria for clinical practice. Primary care physicians diagnose the majority of FM cases rather than subspecialists. Consequently, many physicians rigidly applied the research criteria or rejected their face validity. Accordingly, few providers consistently identified and applied 4 kg of pressure to all 18 designated areas. They used symptom-based diagnostic criteria that focused on fatigue, cognitive impairment, and somatic symptoms, which were excluded from the original research criteria. Moreover, an additional problem with the criteria is that patients with symptom improvement and examination findings no longer met the research classification.

Twenty years after the initial research classification was developed, the FM research community recognized the growing need for clinical diagnostic criteria that reflect the spectrum of FM and practical components of clinical diagnosis. The objective was to develop a screening tool with wide applicability that could be used to diagnose and assess the severity of FM symptoms. Researchers evaluated patients in whom FM was previously diagnosed using the widespread pain index (WPI) and categorical scales. The new criteria, developed in 2010 and revised in 2011 and 2016,[3–5] used these categorical scales to assess patients' cognitive symptoms, unrefreshing sleep, fatigue, and other somatic symptoms.

TABLE 37.1 American College of Rheumatology Criteria for Research Classification of Fibromyalgia

Criterion	Description
1. History	Chronic, widespread (four quadrants) soft tissue pain for three months.
2. Examination	Pain (1+ or greater in severity) induced by 4 kg of digital palpation pressure at 11 of 18 anatomically defined tender points (Table 37.2).
3. 1 and 2 are true	When 1 and 2 are true, sensitivity and specificity for FMS are >80%.

Adapted from Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia report of the multicenter criteria committee. *Arthritis Rheum.* 1990;33:160–172.

FMS, Fibromyalgia syndrome.

The ACR used these categorical scales to develop a severity scale. Finally, they combined the severity scale with the WPI to stratify disease severity in patients with FM (Box 37.1). The diagnostic criteria for fibromyalgia were initially designed by unblinded rheumatologists for research purposes. With the evolution of diagnostics to extend to clinical space, a large proportion of clinically diagnosed fibromyalgia does not meet the research diagnostic criteria.[6] A critical advance in our understanding of fibromyalgia is the evolution to symptom-based diagnosis and elimination of the tender point criteria, reflecting a shift in thinking about the spectrum of FM symptoms.[3]

Prevalence Estimates

FM has been found in all ethnic groups studied to date; it is not limited to affluent or industrialized nations. With prevalence estimates ranging from 2% to almost 12% in the general population, it must be viewed as a common medical condition.[7,8] Its prevalence increases with age, most dramatically in women, with a peak in the fifth to seventh decade (7.4% to 10%). Using the original 1990 criteria, including tender points, women were four to seven times more likely to be affected than men of similar age.[8] This was another unintended consequence of the 1990 ACR criteria, by using the same tenderness threshold in men and women, even though we now understand that women are substantially more tender than men, which overestimates the prevalence of FM in men. Using the newer criteria, the ratio was closer to a 2:1 female:male ratio. In contrast, the sex distribution of childhood FM is almost equal (until puberty, girls have similar levels of tenderness relative to boys). Many children outgrow their symptoms.[9] Fibromyalgia the incidence of fibromyalgia is poorly characterized, but risk factors for its development may include obesity, lack of physical activity, poor life/job satisfaction, physical trauma, a febrile illness, or a family history of FM; these factors may not be mutually exclusive.

Clinical Features

The proposed clinical flow would stratify these patients for improved management (Box 37.2). The clinical manifestations of FM typically involve much more than pain, and in fact, these non-pain symptoms are often the key to differentiating the nociplastic pain of FM from nociceptive or neuropathic pain.

TABLE 37.2 Eighteen Anatomically Defined Tender Points in Fibromyalgia Syndrome

Number	Official American College of Rheumatology Bilateral Tender Point Sites
1, 2	Occiput—suboccipital muscle insertions
3, 4	Low cervical—anterior aspects of the C5-7 intertransverse spaces
5, 6	Trapezius—midpoint of the upper border
7, 8	Supraspinatus—origins above the scapular spine, near the medial border
9, 10	Second rib—upper lateral surface of the second costochondral joint
11, 12	Lateral epicondyle—2 cm distal to the epicondyles
13, 14	Gluteal—upper outer aspect of the buttock, anterior fold of the muscle
15, 16	Greater trochanter—posterior to the trochanteric prominence
17, 18	Knees—medial fat pad, just proximal to the medial condyle

Adapted from Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia report of the multicenter criteria committee. *Arthritis Rheum.* 1990;33:160–172.

The most important manifestation in FM and nociplastic pain is that pain is more widespread and more severe than expected. In the new FM criteria, the widespread nature of pain is assessed by asking individuals if they have pain in 19 different bodily regions; this is scored from zero to 19 depending on how man sites are involved. The comorbid symptoms that are most commonly seen and thus are scored from zero (not present) to three (severe) within the Symptom Severity Index in the new FM criteria are difficulty with sleep, memory, and fatigue, and headaches, irritable bowel syndrome symptoms, and depression are also assessed in this measure and are given one point each toward the total score on this measure. Another set of symptoms that are becoming increasingly understood with a better understanding of the pathophysiology of these conditions is sensory hyper-responsiveness. Individuals with FM are just as sensitive to the loudness of noises or brightness of lights as they are to painful stimuli, and these symptoms of sensory hyper-responsiveness throughout the body (leading to symptoms such as urinary frequency, dry eyes) can be very helpful in identifying this type of pain.

Cognitive Dysfunction

Ranging from difficulty concentrating when reading a book to short-term memory deficits, people with FM frequently complain of diminished cognitive function. Research has suggested that FM patients perform poorly on a range of cognitive tasks[10] and exhibit premature cognitive aging, with the main evidence of abnormality being derived from distraction or multitasking experiments.

Insomnia

Most patients with FM experience chronic insomnia. Some have difficulty falling asleep (initial insomnia), but most awaken feeling distressingly alert after only a few hours of sleep (mid-insomnia)

• Box 37.1 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

1. Criteria

A patient satisfies the diagnostic criteria for fibromyalgia if the following three conditions are met:

1. Widespread pain index (WPI) score >7 and symptom severity (SS) scale score >5 or WPI score of 3 to 6 and SS scale score >9.
2. Symptoms present at a similar level for at least three months.
3. No disorder present that would otherwise explain the pain.

2. Ascertainment

1. WPI: note the number of areas in which the patient experienced pain over the last week. In how many areas has the patient had pain? The score will be between zero and 19.
   Shoulder girdle, left hip (buttock, trochanter), left jaw, left upper part of the back
   Shoulder girdle, right hip (buttock, trochanter), right jaw, right lower part of the back
   Upper part of the arm, left upper part of the leg, left side of the chest, or neck
   Upper part of the arm, right upper part of the leg, right side of the abdomen
   Left lower part of the arm, left lower part of the leg
   Right lower part of the arm, right lower part of the leg
2. SS scale score:
   Fatigue
   Waking unrefreshed
   Cognitive symptoms
3. For each of the three symptoms above, indicate the level of severity over the past week according to the following scale:
   0= No problem
   1= Slight or mild problems, generally mild or intermittent
   2= Moderate: considerable problems, often present and/or at a moderate level
   3= Severe: pervasive, continuous, life-disturbing problems
4. Considering somatic symptoms in general, indicate whether the patient has the following*:
   0= No symptoms
   1= Few symptoms
   2= Moderate number of symptoms
   3= Great deal of symptoms

The SS scale score is the sum of the severity of the symptoms (fatigue, waking unrefreshed, cognitive symptoms) and the extent (severity) of somatic symptoms in general. The final score ranged from 0 to 12.

*Somatic symptoms that might be considered are muscle pain, irritable bowel syndrome, fatigue or tiredness, difficulty thinking or remembering, muscle weakness, headache, pain or cramps in the abdomen, numbness or tingling, dizziness, insomnia, depression, constipation, pain in the upper part of the abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives or welts, ringing in the ears, vomiting, heartburn, oral ulcers, loss of or change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulty, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

• Box 37.2 Proposed Plan for Screening and Comprehensive Care of Patients With Fibromyalgia

1. Phase 1: Pain Screening and Primary Care

Phase 1 involves a simple screening questionnaire in which the receptionist for a primary care health professional (primary care physician [PCP], chiropractor, nurse practitioner, physician assistant, general practitioner, general internist) would give every patient entering the waiting room until all the primary care professionals' regular patients had been assessed (Fig. 37.2). After that, it may be administered only to new patients. When the PCP reviews the form of a patient with pain (question 1 answered "yes"), a decision about the symptom's distribution would be made (localized pain, regional pain, widespread pain). A second decision would be to initiate care for the patient's symptoms or refer the patient for further care of this problem.

2. Phase 2: Comorbidity Screening and Secondary Care

Based on the findings on the screening material, a patient identified as having widespread pain would be examined by the PCP or referral physician to make the diagnosis (fibromyalgia [FM] if it applies). The next stage would be screening for comorbid conditions by a well informed and willing PCP or consultant (rheumatologist, neurologist, pain specialist, internist, physiatrist). The patient began an exercise program and counseling with a professional specifically trained to provide advanced care for FM. Problems found in counseling (e.g. marital, financial, and psychiatric) would spin off to an experienced specialist (e.g. counselor, psychologist, psychiatrist, disability advisor, financial counselor).

3. Phase 3: Comorbidity Screening and Tertiary Care

Based on the second line screening for comorbid conditions, care would begin for additional diagnoses. This phase may invoke referral to tertiary subspecialty care (e.g. cardiologists, gastroenterologists, neurologists, neurosurgeons, physical therapists, psychiatrists, physiatrists, obstetrician-gynecologists, urologists). This care should be integrated with follow up by primary care resources.

4. Phase 4: Long-Term Primary Care and Follow Up Assessment

Primary or secondary healthcare professionals will continue to monitor the patient over time and assess the status of care for pain and comorbid conditions. There would be monitoring for side effects to medications and new problems intruding on the continuity of the FM that might or might not be related to it. In this phase, it is important not to assume that every new symptom in a patient with FM is a component of FM. Healthcare providers need to know what is and is not expected with FM.

and are then unable to sleep soundly again until it is almost morning (terminal insomnia). People with FM typically awaken in the morning feel painfully stiff, cognitively sluggish, and unrefreshed by their sleep.[11]

Stiffness

The morning stiffness experienced by most FM patients is lengthy and severe compared with other mechanisms for morning stiffness. The typical stiffness of osteoarthritis usually lasts 5 to

15 min, whereas that of patients with inflammatory rheumatoid arthritis is 30 min to 2 h. By comparison, the stiffness of FM patients typically lasts from 45 min to 4 h. The best clinical correlate with morning stiffness in FM is pain; therefore patients have challenges distinguishing these constructs from their experiences.

Fatigue

Approximately 80% of FM patients complain of fatigue. Consequently, a large proportion of individuals who meet the criteria for FM also meet the criteria for chronic fatigue syndrome.[12] The differential diagnosis of fatigue is difficult because it must include various sleep disorders, chronic infections, autoimmune disorders, psychiatric comorbidities, and neoplasia. Fatigue may also result from residual levels of prescribed medication, such as tricyclic anti-depressant drugs or other neuropathic medications often used to treat insomnia associated with FM.

Constellations of Previously Diagnosed Comorbid Pain Conditions

There are two sets of comorbid conditions typically seen in association with FM or nociplastic pain: other Chronic Overlapping Pain Conditions (COPCs),[13] that are also predominantly nociplastic pain (e.g. irritable bowel syndrome or tension headache); and other pain conditions that have a different primary pain mechanism (nociceptive or neuropathic pain) wherein nociplastic pain is superimposed. The former category had previously been called primary FM, and the latter category secondary FM or central sensitization.

It may be very important to differentiate primary from secondary FM because, in secondary FM or central sensitization, ongoing nociceptive input or neuropathic damage may be partially driving or maintaining the central sensitization. In these individuals, more aggressively treating the underlying problem might help improve the FM or nociplastic pain, whereas that would not be expected in primary FM, which seems to be more of a top-down brain disorder that typically begins early in life.

Chronic Overlapping Pain Conditions

COPCs appear to be system-based expressions of central sensitization,[14,15] reflecting a range of severities and present on functional neuroimaging and quantitative sensory testing.[16,17] An alternate term previously used was sensory sensitivity symptoms. The spectrum of centrally mediated painful conditions includes headache, facial pain, temporomandibular disorders (TMD), irritable bowel syndrome, dyspepsia, interstitial cystitis, painful bladder syndrome, vulvodynia, endometriosis, and female urethral syndrome. These disorders may have specialist involvement of neurology, dentistry, gastroenterology, urology, or gynecology with a primary diagnosis of one of these centrally sensitizing spectrum conditions.

Neurologic/Dental Sensitization

People with coexisting headaches, facial pain, and TMD may cycle between specialist providers in neurology, dentistry, and pain, but the shared sensitization appears to be consistent across the diagnoses.[18–20] Headache demonstrates overlapping sensitization through shared pathways and treatment responses.[21,22]

Gastrointestinal Sensitization

Irritable bowel syndrome (IBS) and benign dyspepsia are common gastrointestinal conditions that occur in 30% to 50% of patients with FM. A feature common to both FM and IBS may be central sensitization and underlying neuroplastic alterations. These conditions may be synergistic with respect to patients' perceptions of their illness and have a modulating effect on clinical outcomes.

Gynecologic Sensitization

Pelvic pain syndromes may first present to gynecologists, including vulvodynia, dysmenorrhea, and endometriosis. Nevertheless, these disorders are associated with sensitization findings and have a complicated association with stress.[23–25]

Urological Sensitization

Approximately 60% of FM patients experience urinary urgency and nocturia regularly, and there is a high rate of bidirectional comorbidity between interstitial cystitis/painful bladder syndrome and FM. Up to 12% of FM patients also fulfill the diagnostic criteria for female urethral syndrome,[26] which is defined as the presence of urinary frequency, dysuria, suprapubic discomfort, and urethral pain despite sterile urine. Many patients are frequently treated with antibiotics for culture-negative urinary tract infections. Intensive investigations often fail to identify specific causes. Self-report questionnaire instruments were developed to facilitate screening for this condition in patients with FM (Fig. 37.1).[27]

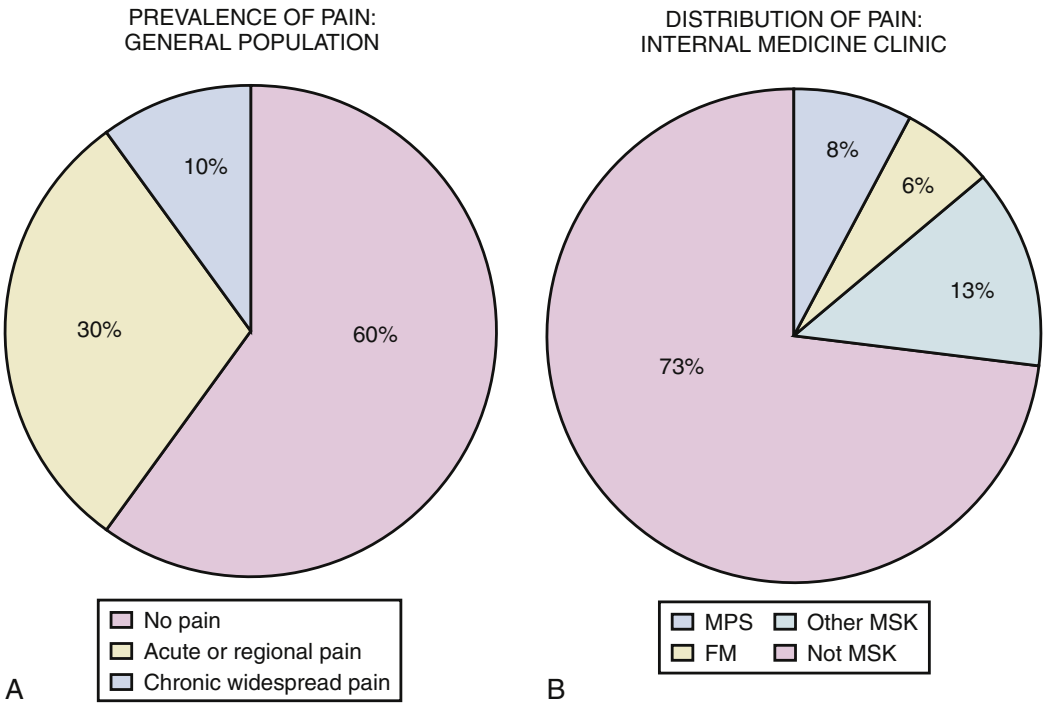
Secondary Fibromyalgia Diagnoses

Conversely, FM can develop in patients with other chronic diseases during the course of their symptoms. In the setting of another painful condition or inflammatory disorder, the FM condition has been referred to as secondary FM. This terminology is not intended to imply that the FM is always caused by the other condition, but the terminology is entrenched and serves a purpose. Secondary FM may not be clinically distinguishable from primary FM,[28] but increasingly, laboratory findings can be used to distinguish these FM subgroups.[29]

As examples of secondary FM, almost 30% of patients with rheumatoid arthritis, 40% of patients with systemic lupus erythematosus, and 50% of those with Sjögren's syndrome have concomitant FM. Patients with rheumatic disease and FM seem to experience articular pain disproportionate to synovitis. This must be considered when treating rheumatic conditions because increasing the dosage of antirheumatic medications in the absence of active inflammation may have little effect on the pain amplified by FM. The best results are obtained by treating each condition separately.

Patients with rheumatic disease and concomitant FM should be warned that a transient increase in FM symptoms may occur with each decrease in glucocorticoid dosage (steroid withdrawal FM). Therefore usual FM therapy may need to be increased transiently. This is a surprising phenomenon because glucocorticoids do not help treat primary FM. To avoid interference with a steroid taper by emergent FM, it is best to decrease the dosage of the glucocorticoid used to treat rheumatic disease in graduated steps at approximately two week intervals. The rate of tapering depends on the current dosage.

Infectious and inflammatory conditions that seem to be associated with FM include hepatitis C, tuberculosis, syphilis, and Lyme disease. The prevalence of overlap may depend on the prevalence of infectious diseases in the community. An academic practice in a Lyme-endemic area evaluated 788 patients with apparent infection for a mean of 2.5 years.[30] Of those with Lyme disease, 20% met the criteria for FM. The symptoms of FM developed one to four months after infection, often associated with Lyme arthritis. The signs of Lyme disease generally resolved with antibiotic



• **Figure 37.1** Prevalence of Pain in the General Population (**A**) and an Academic Internal Medicine Clinic (**B**). *FM*, Fibromyalgia; *MPS*, myopathic pain syndrome; *MSK*, musculoskeletal.

therapy, but FM symptoms often persisted. The largest subgroup of the 788 patients did not have Lyme disease, but they met the criteria for FM or chronic fatigue syndrome.

Pathogenesis

Patients with FM have a constellation of symptoms, but the most common symptom is pain. Before the advent of research techniques such as quantitative sensory testing and functional neuroimaging, many believed that FM and chronic widespread pain had primarily a psychosocial origin with little "organic" basis. However, patients with FM demonstrate reliably augmented sensory processing that was initially thought to be confined to the sensation of pain (i.e. hyperalgesia or allodynia) but is now known to include hypersensitivity to other sensory stimuli such as auditory stimulation.[31,32] Functional magnetic resonance imaging (fMRI) studies have corroborated this finding of hyperalgesia or allodynia in that multiple studies have now shown that FM patients display increased neuronal activation in comparison to controls when the same low-intensity stimulus is applied to both groups.[33] fMRI studies have demonstrated the impact of comorbid psychological factors influencing FM.[34] People with central sensitization conditions, such as FM, appear to have lower thresholds to generate pain responses than in normal controls.[35-37] These imaging studies also provide a theoretical basis for globally augmented sensory processing in FM since the area of the brain that most consistently exhibits increased activity in FM and most other chronic pain states is the insula, a region involved in polysensory integration.[38] Even though multiple mechanisms to assess alterations in pain perception are used, the pressure pain threshold (rather than heat or electrical stimuli) response has the closest relationship with the clinical features of FM and other chronic pain states.

Patients with FM have also been found to have altered levels of biomarkers associated with pain, specifically glutamate and substance P (SP).[39] Harris and colleagues' recent work using proton spectroscopy to evaluate insular glutamate elevations in patients with FM demonstrated higher mean levels than in controls.[40,41] Although such techniques do not allow simple patient testing, the findings support the distinct biologic identity of FM. Endogenous opioid levels are elevated relative to controls, thereby providing a potential mechanism for the lack of responsiveness to opioid therapy in patients with FM, laying the foundation for using low dose naltrexone as a treatment option.[42] Objectively, this has been demonstrated through positron emission tomography (PET)-derived μ-receptor occupancy.[43,44]

Abnormalities in neurochemical mediators of central nervous system (CNS) nociceptive function are present in ways consistent with the patterns of symptoms. The role of neurochemicals as neurotransmitters and modulators of the nociceptive process has been studied extensively in animals.[45] It is believed that these agents participate in the descending inhibition of nociception. This line of reasoning has led to the measurement of neurotransmitter levels in biological fluids obtained from patients with FM. Several major classes of biochemical participants in the nociceptive process are biogenic amines (e.g. serotonin, norepinephrine, and dopamine), excitatory amino acids (e.g. glutamic acid, glutamine, aspartic acid, asparagine, glycine, arginine), neurokinins (e.g. SP, calcitonin gene-related protein, arginine vasopressin, neuropeptide Y), nerve growth factor (NGF), and nitric oxide. Biogenic amines are generally considered antinociceptive, whereas the excitatory amino acids, SP, NGF, and perhaps even nitric oxide are more likely to be pronociceptive.

Another approach to understanding the cause of FM has been through genetic studies. While this is a promising approach to developing personalized treatment paradigms, this is an area of active research. Genetic studies have not yet identified reproducible and strong candidate polymorphisms or haplotypes despite familial associations in people with fibromyalgia. Candidate

Phase 1: Screening Questionnaire

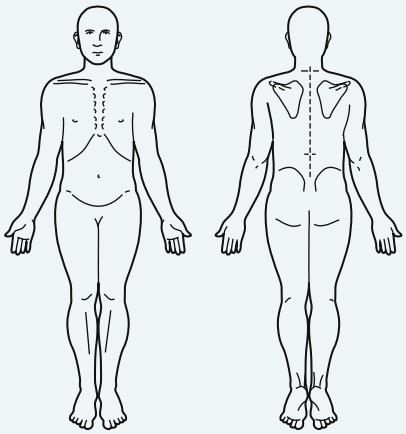
Instructions: Answer yes or no to each of the following questions. If you answer no to question 1, you are done. You do not need to read any of the other questions. When you are done, please return the completed questionnaire to the office clerk.

Yes	No	
☐	☐	1. Have you had body pain for at least three months?
☐	☐	2. Was your body pain one of your reasons for coming to the doctor today?

Instructions: If you answered Yes to question 1, mark a slanted line across the line below to indicate how severe your pain has been over the past two weeks.

No pain — Severe pain

Instructions: If you answered yes to question 1, use a pencil or pen to mark darkly on the body diagrams the locations of your pain during the last week.



Below this line is for office use only. Please do not mark below this line.

- Physician interpretation [check one]:
  ___ Localized ___ Regional ___ Widespread Soft Tissue Pain
- Optional examination findings [indicate values]:
  Total Tender Point Count_____ TPI_____ APT_____
- Referral: ____Yes ____No To _____

• **Figure 37.2** Screening Questionnaire for Chronic Widespread Pain as Seen in Fibromyalgia Syndrome (FM). The findings supportive of FM would be chronic pain from question 1, the relative severity of the pain from question 3, and widespread pain from question 4. Each question could also be applied to other categories of soft tissue pain, and patients with localized or regional musculoskeletal pain, if present, would be identified by the body pain diagram.
APT, Average pain threshold; *TPI*, tender point index.

polymorphisms for fibromyalgia have been inconsistent in studies, including serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine four receptor, and catecholamine *o*-methyl transferase (COMT).[46,47] Epigenetic theories are emerging in mechanistic fibromyalgia research because of their strong association with environmental factors such as stressful experiences.[48] Published studies have documented familial patterns. Some have predicted an autosomal dominant mode of inheritance for FM,[49,50] and evidence for this has increased. In a study by Yunus et al.[51] a linkage of FM with the histocompatibility locus was examined using the sibship method. A complete genome scan of families with two or more FM-affected members has been undertaken by using samples of DNA from a large number of multi-case FM families for comparison of clinical and laboratory genotypic features.[52] Meanwhile, several candidate genes have been proposed to directly explain the specific metabolic abnormalities that have been consistently observed in FM.[53] No evidence for linkage was found in the HTTLPR gene region. Families with an older age of onset were linked to the human leukocyte antigen (HLA) region (logarithm of the odds [LOD] = 3.02, $P = 0.00057$), thus suggesting an immune-mediated pathogenesis. Bioinformatics mining and further sequencing of genes in the HTR2A region will help identify specific polymorphisms for further clinical association testing.

Subsets of patients with FM exhibit functional abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, sympathoadrenal

(autonomic nervous) system, hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-gonadal axis, or hypothalamic-pituitary-growth hormone axis.[54] In FM patients, the HPA axis exhibits an exaggerated adrenocorticotropic hormone (ACTH) response to insulin-induced hypoglycemia or stressful exercise. Despite this dramatic rise in serum ACTH levels in FM, the level of cortisol did not increase commensurately. Mediators that regulate the HPA axis include corticotropin-releasing factor, serotonin, norepinephrine, SP, and interleukin (IL)-6.[55,56]

The reasons why these endocrinopathies are associated with chronic pain syndrome are not entirely clear.[54,56] It may be that CNS abnormalities in the availability of biogenic amines such as serotonin, norepinephrine, and/or dopamine are responsible for the abnormal regulation of the neuroendocrine system.[57] These systems interact and are interdependent, so in susceptible individuals, a partial failure of one system may lead to subtle malfunctions in others. Moreover, immune function abnormalities have been identified as early as the 1980s.[58] This foundation has been expanded to include additional markers. Research on fibromyalgia has spanned the search for serum antinuclear antibodies,[59-61] lymphocyte immune abnormalities,[58] and critically evaluating the role of cytokines such as IL-6 and IL-8.[55,62,63]

In summary, the pathogenesis of FM was shaped by the recognition of allodynia as a manifestation of abnormal central nociceptive processing. This has redirected the collective view of the FM. This revised perspective pointed out research on this condition in a new direction, specifically toward the study of central sensitization. Some abnormalities found in FM are logically consistent with the pain amplification syndrome. The extent to which these mechanisms are unique to FM is critical in determining the direction of future research.

Management Approaches

The objectives of FM treatment are to reduce pain, improve sleep, restore physical function, maintain social interaction, and re-establish emotional balance. A reasonable community objective might be to reduce the need for expensive healthcare resources. To achieve these goals, patients will need a combination of social support, education, physical modalities, and medication. A six-step outline of therapy has been developed; *ADEPT living* stands for attitude, diagnosis, education, physical modalities, treatment with medication, and living.

Attitude

Attitude refers to the preparation or frame of mind that each participant brings to the therapeutic interaction. For clinicians, viewing FM as a neuroinflammatory disorder that creates central sensitization provides a framework for understanding the tremendous impact on the patient's life. From the patient's perspective, it is important to realize that FM is a constellation of symptoms with treatments that require biopsychosocial efforts and participation by the patient. Recognizing and sharing updates and limitations in knowledge regarding FM can help set up a more positive treatment dynamic for clinicians and patients.

Diagnosis

The correct diagnosis should be made to identify FM and disclose any comorbid medical conditions. The management approach will also need to accommodate these other conditions if the patient has concomitant hypothyroidism, diabetes mellitus, or renal insufficiency. For example, when rheumatoid arthritis and FM are evident in the same patient, treatment is more successful when both conditions are treated as though the other is not present. Fibromyalgia is not a diagnosis of exclusion, and patients can have comorbid pain conditions that may benefit from tailored treatment (e.g. low back pain).

Education

Education is crucial for the management of FM. Understanding is crucial for playing an active role in therapeutic programs. Several studies have examined the effects of cognitive behavior therapy (CBT) on outcomes in FM and demonstrated positive effects on pain scores, pain coping, pain behavior, depression, and physical functioning.[64] Such gains are often maintained for several months after completion of the therapy, and periodic booster sessions may prolong the benefits. Joining a resource-oriented support group can help FM patients come to terms with a complicated illness.

Physical Modalities

A variety of physical modalities have been proposed as interventions for FM and can logically be segregated into two categories: those that patients can accomplish for themselves and those that require active participation by a trained therapist. At home, patients can pace their usual activities by setting a clock to time the necessary work activity and then balance the work time with an equal period of rest. Progressive exercise, heat applied as a shower or bath, and Jacobson relaxation techniques can all be used as self-directed therapies with minimal cost.[64]

Aerobic exercise was among the first nonpharmacologic strategies advocated for FM patients, with convincing evidence of benefit.[64] Its goals are to maintain function for everyday activities and to prolong life through cardiovascular fitness. Low-impact exercise, with an intensity sufficient to challenge aerobic capacity, can also reduce pain, improve sleep, balance mood, improve stamina, instill new perspectives, restore cognition, and facilitate a sense of wellbeing.[65] Patients who can exercise sustain a less negative impact of FM in their lives.[66,67] Other recent studies have shown benefits in terms of quality of life and pain in patients involved in exercise programs alone.[68] However, one should be aware that high levels of exertion can temporarily worsen the pain and result in fear of movement (kinesophobia), especially in this patient population. When FM is first diagnosed, the patient is usually deconditioned and has already learned to fear the pain induced by exercise. When prescribing exercise for FM patients, the clinician should begin with low-intensity exercise, such as walking in place in a swimming pool and minimize eccentric muscle contractions.[69] the continuation of the exercise program. Other physical therapies, including yoga,[70] pilates,[71] and tai chi,[72] have been found to be effective in reducing the pain associated with FM. However, other alternative and complementary methods, including Reiki, provided no benefits.[73]

Most patients report benefits from heat in the form of dry or moist heat. Many studies have found that a hot bath or shower can be more effective than analgesic medication for headaches, body pain, and stiffness. The application of heat can relax muscles, facilitate exercise, and improve the sense of wellbeing. Cold applications are preferred by some researchers. Light massage that gradually progresses to deep sedative palpation of large body surfaces can reduce muscle tension, but its influence on body pain usually lasts only one or two days.

Treatments

Cognitive Behavior Therapies

Numerous psychological therapies have been found to be beneficial for pain relief in patients with chronic widespread pain, including

FM. In a recent randomized controlled trial (RCT),[74] telephone-based CBT was found to be beneficial for healthcare related quality outcomes. In this study, 442 patients with chronic widespread pain were randomized to receive six months of telephone CBT, graded exercise, combined intervention, or treatment as usual. Patients receiving CBT with or without exercise performed better than those who underwent standard medical treatment. Those who combined CBT with exercise showed the greatest improvement. These improvements in quality of life were long lasting, and the interventions were cost-effective by using telephone instead of face-to-face CBT. Attention modification has also been very successful in altering the perception of pain in patients with chronic widespread pain. Attention bias refers to the phenomenon whereby patients identify with information that reinforces their focus on their painful condition. The goal of attention modification is to interrupt this negative and self-reinforcing cognitive cycle. In a recent RCT, the Attentional Modification Paradigm (AMP), in which patients completed two 15 min AMP sessions per week for four weeks, was used to facilitate such changes in attentional pain biases.[75] Those in the AMP program reported statistically significant and substantial reductions in several individual difference variables relative to those in the control condition, and a greater proportion experienced clinically significant reductions in pain.

Pharmacotherapies

Recent developments regarding FM therapy relate to new medications being developed and tested specifically for this condition. Three medications, including amine reuptake inhibitors duloxetine and milnacipran, and the membrane stabilizer pregabalin, are currently approved by the Food and Drug Administration (FDA) for the treatment of pain related to FM. Many medications have been used with varying success in an off-label fashion. The theoretical background relating these agents to FM has been based on various biochemical or physiologic abnormalities found in FM,[76-78] and is known to be an important contributor to the pathogenesis of pain. One approach to the therapeutic goals of pharmaceutical therapy would be to say that FM has three main domains (or symptoms) that represent targets for therapeutic intervention, which include pain, insomnia, and depression, but others could be substituted as well.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are not effective as a monotherapy for this condition. Perhaps the more important role of such agents is to contribute to synergy with other medications because it is very likely that some of the central sensitization seen in conditions such as FM is probably driven by peripheral nociceptive input.

Local Anesthetics

Lidocaine infusions have not generally been found to provide supplemental benefit in addition to oral amitriptyline intake for pain outcomes.[79] However, a recent study of 68 FM patients with MPS and 56 FM patients with regional joint pain showed that peripheral TrP injections and hydroelectrophoresis ameliorated FM pain and increased pain thresholds at sites distant from the therapeutic interventions, thus providing further evidence that painful peripheral stimuli contribute to the perpetuation of central augmentation.[80]

Opioids

Although opioids are prescribed for the treatment of FM, clinical experience and empirical evidence indicate that they are not effective in ameliorating this condition.[81,82] Thus the risk of tolerance, opioid-induced hyperalgesia, addiction, and prescription drug diversion is not justified by the insignificant therapeutic benefit. Opioids can disrupt the sleep architecture of people with fibromyalgia, increasing lighter sleep and decreasing slow wave sleep. Sleep disruption can negatively impact symptoms associated with fibromyalgia. The higher the opioid dose, the greater is the sleep quality disruption.[83] The aim of opioids in severe cases and those refractory to all conservative medical and psychological therapies should not be merely pain relief but rather a clear improvement in physical function. If improvement in function is not achieved, these agents must be discontinued and not restarted. A therapeutic trial with a defined endpoint and defined target dose must be discussed with the patient before starting opioid-based therapy. If the physician and patient engage in opioid therapy, a clear behavioral contract needs to be signed by both parties.

Amine Reuptake Inhibitors

Tricyclic anti-depressant (TCA) drugs are effective at low doses (10–150 mg) and improve sleep and enhance the effects of analgesics. Two TCAs that have been extensively studied in FM are amitriptyline (typically administered in doses from 10 to 50 mg) and cyclobenzaprine (typically given in doses from 2.5 to 20 mg) administered at night to improve sleep.

Selective serotonin reuptake inhibitor (SSRI) drugs were developed for the treatment of depression. However, in the usual antidepressant dosages, these agents are effective as monotherapy for depression, and at higher dosages (fluoxetine, 40–50 mg/day), to relieve FM pain.[84] This analgesic effect may be non-serotonin selective at these high doses. The analgesic effects of the tricyclic drugs, not apparent with normal dosages of SSRIs, have suggested that the small contribution from inhibition of the norepinephrine transporter might be critical to their pain-relieving effect. In the tricyclic class, there is a large up to a 900-fold difference between norepinephrine reuptake inhibition activity and that of serotonin.

Another class of amine reuptake inhibitors includes serotonin-norepinephrine reuptake inhibitors (SNRIs), which have been developed to achieve a better balance between the inhibition of the reuptake of serotonin and norepinephrine. One class (exemplified by duloxetine) exhibits almost equivalent activity to SNRI, whereas the other class (norepinephrine selective reuptake inhibitor [NSRI] exemplified by milnacipran) exhibited potent inhibition of norepinephrine reuptake. At dosages of 60 to 120 mg once daily in the morning, duloxetine can be effective in controlling FM body pain, regardless of whether the patient is depressed.[85-87] It is well tolerated by most FM patients. Nausea, dry mouth, constipation, diarrhea, and anorexia are reported more frequently with active drugs than with placebo. The adverse effects can be lessened by starting the drug at a low dosage (30 mg in the morning) and gradually increasing it as tolerated, such as increasing the morning dosage by 30 mg every week. The most common target dose is 60 mg in the evening. However, some studies have noted efficacy at higher doses. Milnacipran is typically administered at doses of 100 to 200 mg daily.[88] Because it is more noradrenergic than duloxetine, it might be helpful in individuals with more prominent fatigue or memory problems, although many individuals have trouble tolerating noradrenergic side effects.

N-Methyl-D-Aspartate Antagonists

The pain amplification of central sensitization can be inhibited or attenuated by *N*-methyl-D-aspartate (NMDA) receptor antagonists. Several NMDA receptor antagonists, including ketamine,

memantine, and dextromethorphan, have been studied in patients with FM and have been shown to have some beneficial effects.[89,90] In the case of ketamine, about 50% of FM patients benefited from an open trial. The concept of FM subgroups was advanced by these findings because ketamine clearly identified responsive and unresponsive subjects from among otherwise comparable FM patients. The usefulness of ketamine as a therapeutic agent for FM has been limited by the fear of adverse effects, such as psychological disturbances (e.g. feelings of unreality, altered body image perception, modulation of hearing and vision), dizziness, anxiety, aggression, and nausea.[91] Furthermore, a more recent trial that examined the long-term analgesic benefit of intravenous ketamine infusions found no benefit of discontinuation of ketamine or at eight weeks following discontinuation.[92] Therefore the benefit of intravenous ketamine infusion may be restricted to its predictive value for dextromethorphan or oral ketamine therapy.[93]

$\alpha_2\delta$ Ligands

Some drugs initially developed as anti-convulsants can raise the threshold for pain fiber depolarization, as they do for central neurons to reduce seizure activity. Pregabalin and gabapentin are ligands for the $\alpha_2\delta$ subunit of voltage-gated calcium channels.[94,95] These compounds have been shown to have anti-hyperalgesic/anti-allodynic, anxiolytic, and anti-convulsant activities in animal models. They reduce the release of several neurochemicals, including glutamate, norepinephrine, and SP. Pregabalin was found to be effective in reducing the severity of body pain, improving quality of sleep, and reducing fatigue in FM patients.[96] Pregabalin is available in the United States but is scheduled as a controlled substance because of its mild anti-anxiolytic activity. At therapeutic dosages (300 to 600 mg/day in two or three divided doses), it was well tolerated. Adverse effects can include dose-related dizziness and somnolence, which resolve despite continuous therapy with the drug. This observation suggests that it is helpful to start at a low dosage and increase it gradually (perhaps weekly) to help the patient adapt. One approach is to start with 100 to 150 mg at bedtime and increase the nighttime dosage weekly to 300 to 450 mg before adding a smaller morning dosage to achieve 450 to 600 mg/day. Weight gain (5–10 lb) and peripheral edema occur in 6% to 12% of patients without any evidence of an effect on the heart or kidneys. Gabapentin has been shown to be effective in FM patients.[97]

Low Dose Naltrexone and Combination Therapies

Low dose naltrexone (LDN), an opioid antagonist, has emerged as a treatment option for fibromyalgia.[42] The mechanistic theory supporting the use of LDN reflects its role as a central anti-inflammatory agent. LDN is used in the range of 1–4.5 mg for these indications.[98,99] The use of specific combinations of newer therapeutic agents, or strategic polypharmacy, has been proposed for the management of FM.[100] It should be noted that there are no published data on the consequences of combining drugs that are effective as monotherapy. The critical principles of this concept for FM are that complementary medications should be from different drug classes, have different mechanisms of action, and not be synergistic for any serious adverse effects.

Procedural Interventions

Surgical interventions for FM pain are not indicated or recommended, and the search for a surgical panacea has resulted in unnecessary or potentially harmful surgical care for patients with chronic widespread pain, including FM. Other non-invasive procedures have been examined for their efficacy in populations with chronic widespread pain.

Other Comorbid Conditions

Dysfunctional Sleep and Fatigue

The bidirectional relationship between sleep and FM is a critical component in identifying strategies to improve pain and function. Focusing on sleep as a goal for improvement may be the first step in targeted therapy. People with fibromyalgia can demonstrate abnormal sleep rhythms, and abnormal sleep rhythms in people without fibromyalgia can cause symptoms that mimic tenderness, myalgia, and fatigue. Poor sleep quality can influence the development of chronic widespread pain states.[101] The management of insomnia in patients with FM remains non-specific and empirical. CBT for insomnia may provide benefits for sleep initiation, maintenance, and perceived quality.[102] The sedating of tricyclic biogenic amine reuptake drugs, such as amitriptyline and cyclobenzaprine, has been the most commonly prescribed medication for FM insomnia. They are not ideal for this role because they cause several adverse effects and are subject to tachyphylaxis, but a one month holiday from all biogenic amine reuptake inhibitors can restore effectiveness.[82] Because SSRIs, SNRIs, and NSRIs are sometimes so stimulatory that they can interfere with sleep, they should be taken in the morning. Two medications used for FM, pregabalin and oxybate, are effective for pain and sleep disturbances.[95,103,104] In addition, both correct the non-rapid eye movement sleep pattern abnormalities seen with FM. Fatigue in FM is probably a direct result of chronic insomnia. Exercise can be an important component in shifting the fatigue cycle.[67] Depression and comorbid conditions, such as sleep apnea, hypothyroidism, diabetes, chronic infection, or anemia, can also drain energy and should therefore be included in the differential diagnosis. Mild exercise can reduce fatigue in patients with FM.

Summary

Despite our evolving understanding of the disease process and increased therapeutic options, patients with chronic widespread pain continue to present diagnostic and management challenges. The disparate range of symptoms found in patients with chronic widespread pain and the multitude of associated comorbid conditions in the patient population contribute to the diagnostic difficulties in an increasingly overburdened healthcare system. Moreover, the most successful treatment modalities require significant personal changes in the behavior and lifestyle of patients, which creates a substantial barrier to implementation. Even the diagnostic criteria for FM are controversial, with researchers and clinicians working to develop a working definition to help identify these patients. The most recent collaboration has resulted in the development of preliminary diagnostic criteria that address symptom severity (Box 37.1).

The clinical manifestations of FM include cognitive dysfunction, affective distress, insomnia, stiffness, musculoskeletal pain, and fatigue. These non-specific symptoms contribute to both the diagnostic and therapeutic challenges of managing FM. Associated comorbid conditions include chronic fatigue syndrome, IBS, interstitial cystitis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. This diverse clinical

picture complicates both the diagnostic specification and burden of individual patient suffering.

The evolution of the pathogenesis of FM is being clarified through molecular studies, sensory testing, and other testing modalities, including functional MRI and PET. Abnormalities in neurochemical biomarkers are being recognized as being associated with FM. Immunologic changes have also been identified through work with ILs and cytokines. Genetic markers (COMT gene) and sex may also play a role in the development of these chronic widespread pain syndromes. The composite result of these novel investigative approaches is an emerging spectrum of identifiable biochemical and functional changes that contribute to chronic widespread pain.

Treatment modalities align with a multi-disciplinary paradigm that includes multiple recent drug developments, cognitive behavior modalities, physical therapy, and exercise programs. Recent changes in FDA-approved pharmacotherapies include the use of pregabalin, as well as the amine reuptake inhibitors duloxetine and milnacipran. The implementation of therapeutic agents is frequently tailored to the patient's symptoms and comorbid conditions (e.g. osteoarthritis vs. insomnia). Ultimately, the most successful treatment outcomes result from multimodal therapy, which relies heavily on patient involvement and investment (physical therapy, exercise regimens, CBT).

Key Points

- The objectives of treatment of fibromyalgia (FM) include reducing pain, improving sleep, restoring physical function, maintaining social interaction, and reestablishing emotional balance. To achieve these goals, patients will need a combination of social support, education, physical modalities, and medication.
- Patients with FM demonstrate reliably augmented sensory processing, which was initially thought to be confined to the sensation of pain (i.e. hyperalgesia and allodynia) but is now known to include hypersensitivity to other sensory stimuli.
- Patients with FM have also been found to have altered levels of biomarkers associated with pain, specifically glutamate and substance P.
- The FDA currently approves three medications for the treatment of pain related to FM: the amine reuptake inhibitors duloxetine and milnacipran, and the membrane stabilizer pregabalin.

Acknowledgments

Portions of this chapter were transcribed or modified from the chapter "Chronic Widespread Pain" by the same authors from the fifth edition of *Practical Management of Pain*.

Suggested Readings

Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain? *Pain.* 2016;157(7):1382–1386.

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38

Headache Management

STEPHEN D. SILBERSTEIN

Introduction

Headache has plagued humans since the beginning of recorded time. It is one of the most common medical complaints and accounts for more than 18 million outpatient visits per year in the United States. More than 1% of physician's office visits and emergency department visits are primarily for headaches.[1,2] In 1988 the International Headache Society (IHS) published a formal classification system for the diagnosis of headache disorders,[3] which has since been updated and improved (International Classification of Headache Disorders, third edition [ICHD-3]).[4] The IHS classification system (Box 38.1) continues to divide headaches into primary and secondary disorders. In a primary headache disorder, headache itself is the illness, and no other etiology is diagnosed. In a secondary headache disorder, headache is attributed to an identifiable structural or metabolic abnormality.

Instruments and Scales in Headache

Headaches can severely interfere with daily functioning and productivity.[5,6] Research has demonstrated that improvement in symptoms and quality of life (QOL) are not perfectly correlated: symptoms may improve, but function may not.[7] Consequently, it is important to embrace instruments that measure QOL. Instruments that assess migraine disability can improve headache care by facilitating physician-patient communication and guiding treatment decisions. Various headache scales are in use. The scales can be divided into two main groups: scales that measure the impact of a single migraine attack (with or without therapy) over a 24 h period and scales that measure the impact of migraine over a span of weeks or months. The first group of scales has been used in randomized, placebo-controlled trials; they are highly sensitive to acute treatment effects.[8] The second group of scales has been chosen to compare results in randomized trials.[9]

Scales that measure the impact of an acute attack include (1) QOL (Migraine-Specific Quality of Life Questionnaire [MQoLQ] and Quality of Life Questionnaire [MSQ Version 2.1]) and (2) headache impact and disability (Headache Needs Assessment [HANA] Survey). Scales that measure long-term impact are (1) QOL (Migraine-Specific Quality of Life [MSQOL] Scale), (2) headache impact (Headache Impact Test [HIT], Headache Impact Questionnaire [HimQ], and Henry Ford Hospital Disability Inventory [HDI]), and (3) migraine disability (Migraine Disability Assessment [MIDAS]).

Scales that Assess Quality of Life

QOL is influenced by environmental, economic, social health-related, spiritual, and political factors. The fundamental domains of instruments that measure QOL include physical, psychological, and social areas. Both generic and disease-specific measures have been used to measure QOL. The most commonly used generic scales are the Medical Outcomes Study (MOS) instrument, which includes the 20 item Short Form Health Survey (SF-20),[10] the SF-36, and the SF-12.[11] Other generic QOL scales used in headache studies include the Sickness Impact Profile,[12] the Nottingham Health Profile,[13] and the Psychological General Wellbeing Index.[14] The specific QOL scales for migraine fall into two broadly defined categories: those that measure QOL in a single migraine attack (MQoLQ and MSQ version 2.1) and those that measure the QOL over a period of weeks or months (MSQOL).

Migraine-Specific Quality-of-Life Questionnaire

The MQoLQ is a questionnaire that assesses the short-term decrements in QOL associated with acute migraine headache attacks.[15] This questionnaire evaluates QOL impairment in the 24 h period following the onset of a migraine headache. The questionnaire is self-administered and is completed quickly and easily. The MQoLQ consists of 15 items with five domains: (1) work functioning, (2) social functioning, (3) energy/vitality, (4) migraine headache symptoms, and (5) feelings and concerns. There are three items within each domain. The response option for each of the items is on a seven point scale, with one indicating maximum impairment of QOL and seven indicating no impairment. Each domain has a maximum score of 21 and a minimum score of three. The scores were compared between migraine-free and migraine periods. The construct validity of the questionnaire was established by showing that there are significant relationships between subjects' 24 h MQoLQ scores and other indices of clinical migraine headache such as headache severity, limitation of activity, number of associated migraine symptoms, global change in migraine symptoms, and migraine duration.[15] The ability of the MQoLQ to capture within-subject change in QOL was evaluated by comparing QOL scores during a "migraine-free" period with MQoLQ scores 24 h after migraine onset.[8] The MQoLQ should be applicable to all adults suffering from episodic migraine headaches. It was designed primarily for use in clinical trials to assess migraine management and to be responsive to subject changes in QOL in the 24 h following the onset of a migraine headache. The

• Box 38.1 International Headache Society Criteria (ICHD-3)

- Migraine
  - Migraine without aura
  - Migraine with aura
    - Migraine with typical aura
    - Migraine with brainstem aura
    - Hemiplegic migraine
    - Retinal migraine
  - Chronic migraine
  - Complications of migraine
- Status migrainosus
- Persistent aura without infarction
- Migrainous infarction
- Migraine aura triggered seizure
- Episodic syndromes that may be associated with migraine
- Tension-Type Headache
  - Infrequent episodic tension-type headache
  - Frequent episodic tension-type headache
  - Chronic tension-type headache
- Cluster Headache and Other Trigeminal Autonomic Cephalalgias
  - Cluster headache
  - Paroxysmal hemicrania
  - Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
  - Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
  - Hemicrania continua
- Other Primary Headaches
  - Primary cough headache
  - Primary exercise headache
  - Primary headache associated with sexual activity
  - Primary thunderclap headache
  - Cold stimulus headache
  - External-pressure headache
  - Primary stabbing headache
  - Nummular headache
  - Hypnic headache
- New Daily Persistent Headache (NDPH)
- Secondary Headaches
  - Headache attributed to head and/or neck trauma
  - Headache attributed to cranial or cervical vascular disorders
  - Headache attributed to nonvascular intracranial disorders
  - Headache attributed to a substance or its withdrawal
  - Headache attributed to infection
  - Headache attributed to a disorder of homeostasis
  - Headache or facial pain attributed to a disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure
  - Headache attributed to a psychiatric disorder
  - Cranial neuralgias and central causes of facial pain

ICHD-3, International Classification of Headache Disorders, second edition.

MQoLQ assesses subjective wellbeing and daily ability to function, in addition to measuring the typical associated symptoms of migraine, such as nausea, photophobia/phonophobia, and head pain. The 24 h MQoLQ should not be used to measure global QOL between headache episodes.

Quality-of-Life Questionnaire (MSQ Version 2.1)

The MSQ is a disease-specific QOL instrument with three hypothesized scales; it has been developed, tested, and revised.[16] The MSQ (version 2.1) was structured similarly to older versions of the MSQ (versions 1.0 and 2.0). The revised 14 item MSQ (version 2.1) consists of seven items in the role-restrictive dimension that measure the degree to which performance of normal activities is limited by migraines, four items in the role-preventive dimension that measure the degree to which performance of normal activities is interrupted by migraines, and three items in the emotional function dimension that measure the emotional effects of migraine.[16] The MSQ dimensions had low to modest correlations with the two component scores of the SF-36 and were modestly to moderately correlated with migraine symptoms. The validation was structured in three separate analyses applied to 267 subjects.[17] The MSQ provides clinicians, researchers, and those who fund health care a measurement tool to assess health-related QOL. The questionnaire was designed to be completed quickly and easily in a self-administered form. This study suggested that the mean MSQ (version 2.1) scores six to 12 points higher (indicating better QOL).

Migraine-Specific Quality-of-Life Scale

The MSQOL is used to assess a migraine patient's QOL over a long period (average of three weeks). It is a valid and reliable self-administered measure and a useful tool in clinical migraine research.[18] The information that MSQOL provides can add important information about migraine's impact on QOL and the potential benefits of therapeutic interventions. This questionnaire has 25 items, with each question having four answers. The general format and scoring are one, very much; two, quite a lot; three, a little; and four, not at all. The total score is then transferred to a scale of zero to 100, with a higher number representing a better QOL. For the MSQOL, Cronbach's alpha was 0.92, suggesting that the items are tapping into a single concept. The MSQOL can provide valuable information on a migraineur's QOL and be a useful adjuvant measure when assessing long-term treatment outcomes.

Scales that Assess Headache Impact and Disability

Headache impairs physical, social, and emotional functioning, but a diagnosis cannot always be made despite the availability of helpful tools. One reason for this is poor patient-physician communication. If the impact that headaches are having on a person's life can be communicated adequately to the physician, the likelihood of appropriate management will increase.[19] Impact and disability instruments are scored differently and have different interpretations. Generally, the impact is scaled in a positive direction, with higher scores reflecting better QOL (i.e. lower impact). For disability measures, higher scores reflect a greater limitation of activity (i.e. higher impact). Measurement of headache-related disability, together with assessments of pain intensity, headache frequency, tiredness, alterations in mood, and cognition, can be used to assess the impact of migraine on sufferers' lives and on society.[20] The tools currently used for assessing headache impact are the HIT and HIT-6, HimQ, HANA Survey, and HDI or Henry Ford Hospital Questionnaire. These scales, when used properly, can improve communication between patients and physicians, assess migraine severity, and act as outcome measures to monitor treatment efficacy. Impact tools are also used, along with other clinical assessments, to produce an individualized treatment plan.[20] Disability measures assess impairment in role functioning (i.e. reduced ability to function in defined roles, such as

paid work).[6] The disability instruments used are the HDI and the MIDAS.

Headache Impact Test

The HIT is a tool that measures headache's impact on a person's ability to function on the job, at home, and in social situations. The HIT was developed by the psychometricians who developed the SF-36 health assessment. HIT was designed for greater accessibility (on the Internet at www.headachetest.com and www.amlhealthy.com and as a paper-based form known as HIT-6). HIT-6 is a practical test that consists of six questions. A patient can complete the test in less than 2 min. HIT-6 assesses disability over a four week period. The range of scores is 36 to 78. Higher scores signify the greater impact of disability. A score of 60 or higher indicates a severe impact (the headache stops family, work, school, or social activities), a score between 56 and 59 indicates a substantial impact, a score between 50 and 55 signifies some impact, and a score below 49 denotes no impact.[21] The availability of this test on the Internet, with feedback provided, makes it a useful tool to help headache sufferers understand the burden of their migraines and seek appropriate management.

Headache Impact Questionnaire

The HimQ measures pain and limitations in activity over a three month period. This instrument was the precursor to the MIDAS instrument (see disability scales). The HimQ score is derived from four frequency-based questions (i.e. number of headaches, missed days of work, missed days of chores, or missed days of non-work-related activity) and four summary measures of the average experience across headaches (i.e. average pain intensity and average reduced effectiveness when having a headache at work, during household chores, and in non-work-related activity).[22,23] This scale was validated after assessing the pain and limitations in activity in a population-based sample of 132 migraine headache sufferers enrolled in a 90 day daily-diary study who completed the HimQ at the end of the study. Previous studies of the validity of retrospective pain and disability reporting were mixed.[22,24–31] Study participants completed the HimQ in person and then completed daily diaries for 90 days. The HimQ was developed to identify headache sufferers who have the greatest need for medical care. Self-administered questionnaires can adequately capture information to rate pain severity.

Headache Needs Assessment Survey

The HANA questionnaire was designed to assess two dimensions (frequency and bothersomeness) of migraine's impact.[32] Seven issues related to living with migraine were used as ratings of frequency and bothersomeness. Validation studies were performed in a Web-based survey, a clinical trial responsiveness population, and a retest reliability population. Headache characteristics (e.g. frequency, severity, and treatment), demographic information, and the HDI were used for external validation. The HANA can be used in medical practice groups (e.g. headache centers, managed care groups) as a screening tool to detect potential problems. Scores from the scale are compared before and after treatment to determine the headache's impact. Primary care physicians could use the HANA to screen patients with a migraine for further evaluation. Once identified, those with severe migraines may be candidates for further evaluation and immediate treatment. The HANA has several advantages in that it can (1) select who should be treated, (2) increase productivity by adequately treating headaches, and (3) identify the need for aggressive treatment without the usual slow advancement through stepped-care algorithms. This brief, self-applied questionnaire may be a useful screening tool to evaluate migraine's impact. The two-dimensional approach to patient-reported QOL allows individuals to weigh the impact of both frequency and bothersomeness of chronic migraine (CM) on multiple aspects of daily life.

Henry Ford Hospital Disability Inventory

The HDI is useful in assessing the impact of headaches and its treatment on daily living.[33–36] It is a paper-and-pencil instrument that probes the functional and emotional effects of headaches on everyday life. The HDI is a 25 item headache disability inventory, with each item requiring a "yes" (four points), "sometimes" (two points), or "no" (zero points) response. Therefore a maximum score of 100 points reflects severe self-perceived headache disability. The scale is easy to complete and simple to score and interpret. The HDI has high internal consistency, reliability, and good content validity; the long-term (two month) test-retest stability of the HDI was robust.[33,34] The test-retest reliability for the beta-HDI was acceptable for the total score and functional and emotional subscale scores.[33] Scales of this nature help investigators understand headache's impact on everyday life. Therefore the HDI can be used to (1) assess the impact of headache on the patient's daily living, (2) monitor the effect of therapeutic intervention, and (3) plan for a global approach to coping with headache with the patient's involvement.

Migraine Disability Assessment Questionnaire

The MIDAS questionnaire (Fig. 38.1) was developed to measure headache-related disability and improve doctor–patient communication about the functional consequences of migraines. The questionnaire was based on five disability questions that focus on lost time in three domains: schoolwork or work for pay; household work or chores; and family, social, and leisure activities.[37] This scale can be used by physicians, nurses, pharmacists, and alternative practitioners. It is easy to complete and takes only a few minutes. The MIDAS questionnaire has demonstrated reliability,[38] as reported in two separate population-based studies, one in the United States and one in the United Kingdom, and validity by using a three month daily-diary study as the "gold standard."[39] Scores on the MIDAS are highly correlated with physician judgments about the severity of illness and the need for treatment.[40] This instrument is scored as follows: a score of 5–10 indicates little or no disability, 10–20 indicates moderate disability, and higher than 20 indicates severe disability. The MIDAS questionnaire is an important part of a package of educational, investigative, and therapeutic measures and could play a major role in improving the care of patients with migraines and other types of headaches.[20,41–48] A randomized, placebo-controlled trial showed that the MIDAS grade provides a basis for selecting initial treatment in stratified care.[49]

Migraine

Migraine is a chronic neurologic disease characterized by episodic attacks of headache and associated symptoms. "Migraine" is derived from the Greek word "hemicrania" (Galen ≈200 A.D).[50]

Instructions: Please answer the following questions about ALL your headaches you have had over the last three months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last three months.

1 On how many days in the last three months did you miss work or school because of your headache? ☐☐

2 How many days in the last three months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.) ☐☐

3 On how many days in the last three months did you not do household work or go to school because of your headache? ☐☐

4 How many days in the last three months was your productivity in household work reduced by half or more because of your headache? (Do not include days you counted in question three where you did not do household work.) ☐☐

5 On how many days in the last three months did you have a headache? (If a headache lasted more than 1 day, count each day.) ☐☐

Total days ☐☐

A On how many days in the last three months did you have a headache? (If a headache lasted more than one day, count each day.) ☐☐

B On a scale of 0-10, on average how painful were these headaches (where 0 = no pain at all and 10 = pain as bad as it can be). Once you have filled in the questionnaire, add up the total number of days from questions 1-5 (ignore A and B). ☐☐

Grading system for the MIDAS questionnaire:

Grade Definition	Score	
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

• **Figure 38.1** MIDAS questionnaire.[37]

The diagnosis is based on retrospective reporting of headache characteristics and associated symptoms.[51] The revised IHS diagnostic criteria for headache disorders[3] (ICHD-2) provide the criteria for a total of seven subtypes of migraine.[4]

Epidemiology

The prevalence of migraines is similar and stable in Western countries and the United States.[52] Three large-scale population-based studies have been conducted in the United States, one in 1989,[53,54] one in 1999,[55,56] and one in 2004.[57,58] The first American Migraine Study[53] found that the prevalence of migraine was 17.6% in women and 6% in men. Two follow-up studies, the American Migraine Study II and the American Migraine Prevalence and Prevention Study (AMPPS), provided results identical to the first, indicating that the prevalence of migraine has been stable in the United States, at least over the last 15 years.[58]

Before puberty, the prevalence of migraine is approximately 4%[58]; after puberty, it increases more rapidly in girls than in boys. It increases until approximately 40 years of age and then declines. Prevalence is lowest in Asian Americans, intermediate in African Americans, and highest in Caucasians.[6] In the United States, the prevalence of migraines decreases as household income increases.[6,53,56]

Migraines decrease the sufferers' QOL. The World Health Organization (WHO) ranks migraine among the world's most disabling medical illnesses.[59] Approximately 28 million Americans have severe, disabling migraine headaches.[55] Migraine's cost to employers is approximately $13 billion per year, and annual medical costs exceed $1 billion.[6] Instruments to quantify migraine disability include the MIDAS[39] and the HIT.[21]

Description of the Migraine Attack

The migraine attack can consist of premonitory, aura, headache, and resolution phases. Premonitory symptoms occur in 20% to 60% of migraineurs, hours to days before the onset of the headache. They may include psychological, neurologic, constitutional, or autonomic features, such as depression, cognitive dysfunction, and bouts of food craving.[60]

Aura

The migraine aura consists of focal neurologic symptoms that precede, accompany, or (rarely) follow an attack. Aura usually develops over a period of 5 to 20 min and lasts less than 60 min. The aura can be visual, sensory, or motor and may involve language or brainstem disturbances.[3] Headache usually follows within 60 min of the end of the aura. Patients can have multiple aura types: most patients with a sensory aura also have a visual aura.[61] Simple auras include scotomata (loss of vision), simple flashes (phosphenes), specks, geometric forms, and shimmering in the visual field. More complicated visual auras include teichopsia or fortification spectra (the characteristic aura of migraine), metamorphopsia, micropsia, macropsia, zoom vision, and mosaic vision. Paresthesias are often cheiro-aural: numbness starts in the hand, migrates up the arm, and jumps to involve the face, lips, and tongue.[51,62] Weakness is rare, occurs in association with sensory symptoms, and is unilateral.[63] Apraxia, aphasia, agnosia, states of altered consciousness associated with déjà vu or jamais vu, and elaborate dreamy, nightmarish, trance-like, or delirious states can occur.[60]

Headache Phase

The median migraine attack frequency is 1.5 per month.[53] The typical headache is unilateral, of gradual onset, throbbing (85%),[64] moderate to marked in severity, and aggravated by movement.[3] Pain may be bilateral (40%) or start on one side and become generalized. It lasts 4 to 72 h in adults and 2 to 48 h in children.[3]

Anorexia is common. Nausea occurs in almost 90% of patients, whereas vomiting occurs in about a third.[65] Sensory hypersensitivity results in patients seeking a dark, quiet room.[51,65] Blurry vision, nasal stuffiness, anorexia, hunger, tenesmus, diarrhea, abdominal cramps, polyuria, facial pallor, sensations of heat or cold, and sweating may occur. Depression, fatigue, anxiety, nervousness, irritability, and impairment of concentration are common. Symptom complexes may be generated by linked neuronal modules.[66]

Formal Diagnostic Criteria

The IHS subdivides migraine into migraine with aura (Box 38.2) and migraine without aura (Box 38.3).[4] To diagnose migraines without aura, five attacks are needed. No single feature is mandatory, but recurrent episodic attacks must be documented.[3] Migraine persisting for more than three days defines "status migrainosus."[3,4] Migraine occurring 15 or more days per month is called CM by the ICHD-3 (Box 38.4).[67]

• Box 38.2 Diagnostic Criteria for Migraine With Aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least three of the following six characteristics:
   1. at least one aura symptom spreads gradually over ≥5 min
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5-60 min[1]
   4. at least one aura symptom is unilateral[2]
   5. at least one aura symptom is positive[3]
   6. the aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

• Box 38.3 Diagnostic Criteria for Headache Without Aura

A. At least five attacks fulfilling criteria B to D
B. Headache attacks lasting 4 to 72 h and occurring less than 15 days/month (untreated or unsuccessfully treated)
C. Headache with at least two of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe intensity
   4. aggravated by or causing avoidance of routine physical activity (i.e. walking or climbing stairs)
D. During headaches, at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and/or phonophobia
E. Not attributed to another disorder

• Box 38.4 Revised International Headache Society Criteria for Chronic Migraine

A. Headache on 15 or more days per month for at least three months and Fulfilling criteria B and C
B. Patient has had at least five attacks fulfilling criteria B to D for *migraine without aura* (see Box 38.3)
C. On eight or more days per month for at least three months, fulfilling any of the following:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

Migraine with aura is subdivided into typical aura, prolonged aura, hemiplegic migraine, basilar-type migraine, and migraine with acute-onset aura. The IHS classification now allows the association of aura with other headache types. Prolonged aura lasts from 1 h to one week, and persistent aura lasts for more than one week (but resolves); if neuroimaging demonstrates a stroke, a migrainous infarction has occurred.

Migraine Variants

Basilar-type migraine aura is characterized by brainstem symptoms: ataxia, vertigo, tinnitus, diplopia, nausea and vomiting, nystagmus, dysarthria, bilateral paresthesia, or a change in the level of consciousness and cognition.[3] It should be considered when patients have paroxysmal brainstem disturbances. Some have suggested that hemiplegic migraines should be diagnosed if weakness is present.[63]

Ophthalmoplegic migraine is caused by idiopathic inflammatory neuritis.[68] There is an enhancement of the cisternal segment of the oculomotor nerve, followed by resolution over several weeks as the symptoms resolve.

Hemiplegic migraines can be sporadic or familial.[51] Attacks are frequently precipitated by a minor head injury.[63] Familial hemiplegic migraine (FHM) is an autosomal dominant, genetically heterogeneous disorder with variable penetration. FHM includes attacks of migraine without aura, migraine with typical aura, and episodes of prolonged aura, fever, meningismus, and impaired consciousness.[69] Headache may precede the hemiparesis or be absent. The onset of hemiparesis may be abrupt and simulate a stroke. In 20% of unselected FHM families, patients have cerebellar symptoms and signs (nystagmus, progressive ataxia). All have mutations in the *CACNA1A gene*.[70]

Treatment

Migraine varies widely in its frequency, severity, and impact on patients' QOL. A treatment plan should consider the patient's diagnosis, symptoms, and any coexistent or comorbid conditions, and the patient's expectations, needs, and goals.[71] Migraine treatment begins with making a diagnosis,[51] explaining it to the patient, and developing a treatment plan that considers any coincidental or comorbid conditions.[72] Comorbidity indicates an association between two disorders that is more than coincidental.[1]

Conditions that occur in migraineurs with a higher prevalence than would be expected include stroke, myocardial infarction, angina, patent foramen ovale (aura), epilepsy, Raynaud's syndrome, and affective disorders (depression, mania, anxiety, and panic disorder). Possible associations include essential tremor, mitral valve prolapse, and irritable bowel syndrome.

Pharmacologic treatment of migraine may be acute (abortive) or preventive (prophylactic), and patients with frequent, severe headaches often require both approaches. Acute treatment attempts to relieve or stop the progression of an attack or the pain and impairment once an attack has begun. It is appropriate for most attacks and should be used a maximum of two to three days per week. Preventive therapy is given, even in the absence of a headache, in an attempt to reduce the frequency, duration, or severity of attacks. Additional benefits include improving responsiveness to acute attack treatment, improving function, and reducing disability.

Treatment for Acute Migraine Headache

Acute treatment can be specific (ergots, triptans, gepants [small molecule calcitonin gene related peptide [CGRP] receptor antagonists], and lasmiditan [selective $5HT_{1F}$ selective agonist]) or nonspecific (analgesics and opioids). Non-specific medications control the pain of migraines and other pain disorders, whereas specific medications are effective for migraine (and certain other) headache attacks but are not useful for non-headache-related pain disorders. Specific treatments are effective for mild, moderate, and

severe migraine attacks.[73] Devices approved for acute migraine treatment include vagal nerve stimulation (VNS), Nerivio (conditioned pain modulation), and Cefaly (transcutaneous stimulation of the area above the nose).

The choice of treatment depends on attack severity and frequency, associated symptoms, coexistent disorders, previous treatment response, and the medication's efficacy and potential for overuse and adverse events (AEs). A non-oral route of administration and an antiemetic should be considered when severe nausea or vomiting is present.[74] Injections can provide rapid relief. Headaches can be stratified by severity and disability, using the MIDAS or the HIT. Analgesics are used for mild to moderate headaches.[74] Triptans, gepants, lasmiditan, and dihydroergotamine (DHE) are first-line drugs for severe attacks and less severe attacks that do not adequately respond to analgesics.[74] Patients with moderate or severe headaches and moderate or severe disability (based on the MIDAS) who were stratified to treatment with a triptan did better than patients given aspirin and metoclopramide.[75]

Early intervention prevents escalation and may increase efficacy.[76] Triptans can prevent the development of cutaneous allodynia, and the presence of cutaneous allodynia predicts triptans' effectiveness.[77] Before deciding that a drug is ineffective, at least two attacks should be treated with that modality. It may be necessary to add an adjuvant or change the dose, formulation, or route of administration. If the response is inadequate, the headache recurs, or AEs are bothersome, a change in medication may be needed. Limiting acute treatment to two to three days a week can prevent medication overuse headache (MOH). When headaches are very frequent, early intervention may not be appropriate.

All treatments occasionally fail. Therefore rescue medications (opioids, neuroleptics, and corticosteroids) are potentially needed. They provide reliable relief but often limit function because of sedation or other AEs.

Preventive Treatment

Preventive therapy is given in an attempt to reduce the frequency, duration, or severity of attacks. Additional benefits include improving responsiveness to acute attack treatment, improving function, and reducing disability. Preventive treatment may avert episodic migraine's progression to CM and result in reductions in healthcare costs. Silberstein and colleagues retrospectively analyzed resource utilization information in a large claims database. The addition of migraine preventive drug therapy to therapy that consisted of only an acute medication was effective in reducing resource consumption. When the six months after the initial preventive medication was compared with the six months preceding preventive therapy, office and other outpatient visits with a migraine diagnosis decreased by 51.1%, emergency department visits with a migraine diagnosis decreased by 81.8%, computed tomography (CT) scans with a migraine diagnosis decreased by 75.0%, magnetic resonance imaging (MRI) with a migraine diagnosis decreased by 88.2%, and other migraine medication dispensing decreased by 14.1%.[78]

Preventive medications reduce attack frequency, duration, and severity.[51,79] According to the United States Headache Consortium Guidelines,[80] as recently revised,[81] indications for preventive treatment include:

- recurring migraine that significantly interferes with the patient's QOL and daily routine despite acute treatment;
- failure of, contraindication to, or troublesome AEs from acute medications;
- acute medication overuse;
- very frequent headaches (>1/week) (risk for CM or medication overuse);
- patient preference; and
- special circumstances such as hemiplegic migraine; frequent, very long, or uncomfortable auras; or attacks with a risk for permanent neurologic injury.

Prevention is not being used to the extent that it should be. Results from the American Migraine Study I and II and the Philadelphia Phone Survey 2 demonstrated that migraine preventive therapy is underused: only 13% of all migraineurs currently use preventive therapy to control their attacks.[58] In the American Migraine Study II, 25% of all people with migraine, or more than seven million people, experienced more than three attacks per month, and 53% of those surveyed reported either having severe impairment because of their attacks or needing bed rest.[56] According to the AMPPS, 38.8% of patients with migraines should be considered for (13.1%) or offered (25.7%) migraine preventive therapy.[82]

Preventive medication groups include β-adrenergic blockers, anti-depressants, calcium channel antagonists, anti-convulsants, CGRP antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs). The choice is based on efficacy, AEs, and coexistent and comorbid conditions. The drug chosen is started at a low dose and increased slowly until therapeutic effects develop or the ceiling dose is reached. A full therapeutic trial may take two to six months. Acute headache medications should not be overused. Because of potential teratogenicity with some of these prophylactic medications, women of childbearing potential should be on adequate contraception.

Preventive treatment is often recommended for only six to nine months, but until now, no randomized, placebo-controlled trials have been performed to investigate migraine frequency after preventive treatment has been discontinued. Diener and associates[83] assessed 818 migraine patients who were treated with topiramate for six months to see the effects of discontinuation of topiramate. Patients received topiramate in a 26 week open-label phase. They were then randomly assigned to continue this dose or switch to a placebo for a 26 week, double-blind phase. The mean increase in the number of migraine days was greater in the placebo group (1.19 days in four weeks, 95% confidence interval [CI] = 0.71 to 1.66, $P < 0.0001$) than in the topiramate group (0.10, −0.36 to 0.56, $P = 0.57$). Patients in the placebo group had more days on acute medication than those in the topiramate group (mean difference between groups: −0.95, −1.49 to −0.41, $P = 0.0007$). Sustained benefit was reported after topiramate was discontinued, although the number of migraine days did increase. These findings suggest that patients should be treated for six months with the option to continue for 12 months. If headaches are well controlled, medication can be tapered and discontinued. Dose reduction may provide a better risk-to-benefit ratio.

Behavioral and psychological interventions used for prevention include relaxation training, thermal biofeedback combined with relaxation training, electromyography biofeedback, and cognitive behavior therapy.[84] Devices include gammaCore (non-invasive VNS), the Nerivio Migra device (non-invasive electronic device worn on the upper arm, which is operated through a mobile application and looks like a sports armband), and the Cefaly device (external trigeminal nerve stimulation device [e-TNS] placed on the forehead).

Coexistent diseases have important implications for treatment. In some instances, two or more conditions may be treated with a single drug. If individuals have more than one disease, certain categories of treatment may be relatively contraindicated.

The preventive medications with the best documented efficacy are divalproex, topiramate, and β-blockers, and the CGRP antagonists. The choice is based on a drug's proven efficacy, the physician's informed belief about medications not yet evaluated in controlled trials, the drug's AEs, the patient's preferences, the headache profile, and the presence or absence of coexisting disorders.[51] The drug chosen should have the best risk-to-benefit ratio for the individual patient and take advantage of the drug's side effect profile.[85,86] An underweight patient would be a candidate for one of the medications that commonly lead to weight gain, such as a tricyclic anti-depressant (TCA); in contrast, one would try to avoid these drugs and consider topiramate if the patient is overweight. Tertiary TCAs that have a sedating effect would be useful at bedtime for patients with insomnia. Older patients with cardiac disease or patients with significant hypotension may not be able to use TCAs, calcium channel blockers, or β-blockers but could use divalproex or topiramate. Athletic patients should use β-blockers with caution. Medications that can impair cognitive functioning should be avoided when patients are dependent on their faculties.[85,86]

Comorbid and coexistent diseases have important implications for treatment. The presence of a second illness provides therapeutic opportunities but also imposes certain therapeutic limitations. In some instances two or more conditions may be treated with a single drug. However, there are limitations to using a single medication to treat two illnesses. Giving a single medication may not treat two different conditions optimally: although one of the two conditions may be treated adequately, the second illness may require a higher or lower dose. Therefore the patient is at risk for the second illness not being treated adequately. Therapeutic independence may be needed should monotherapy fail. Avoiding drug interactions or increased AEs is a primary concern when using polypharmacy. For some patients, a single medication may adequately manage any comorbid conditions. However, this is likely to be the exception rather than the rule. Polytherapy may enable therapeutic adjustments based on the status of each illness. TCAs are often recommended for patients with migraines and depression.[87] However, appropriate management of depression often requires higher doses of TCAs, which may be associated with more AEs. A better approach might be to treat the depression with a selective serotonin reuptake inhibitor or selective serotonin-norepinephrine reuptake inhibitor and treat the migraine with an anti-convulsant. Migraine and epilepsy[88] may both be controlled with an antiepileptic drug, such as topiramate or divalproex sodium. Divalproex and topiramate are the drugs of choice for a patient with migraine and bipolar illness.[89,90] When individuals have more than one disease, certain categories of treatment may be relatively contraindicated. For example, β-blockers should be used with caution in a depressed migraineur, whereas TCAs or neuroleptics may lower the seizure threshold and should be used with caution in an epileptic migraineur.

Although monotherapy is preferred, it is sometimes necessary to combine preventive medications. Anti-depressants are often used with β-blockers or calcium channel blockers, and topiramate or divalproex sodium may be used in combination with any of these medications. Pascual and colleagues[91] found that combining a β-blocker and sodium valproate could lead to increased benefit in patients with migraines previously resistant to either drug alone. Fifty-two patients (43 women) with a history of episodic migraine with or without aura and previously unresponsive to β-blockers or sodium valproate monotherapy were treated with a combination of propranolol (or nadolol) and sodium valproate in an open-label fashion. Fifty-six percent had a greater than 50% reduction in migraine days. This open trial supports the practice of combination therapy. Controlled trials are needed to determine the true advantage of this combination treatment in patients with episodic migraine and CM.

With the advent of monoclonal antibodies against CGRP and its receptor, we have a class of medications with good safety tolerability and efficacy. The four anti-CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, and galcanezumab) are safe, effective, and approved to prevent episodic migraine, CM, and MOH.[92]

Summary

Migraine is an extremely common neurobiologic headache disorder that is caused by increased central nervous system excitability. It ranks among the world's most disabling medical illnesses. Diagnosis is based on the headache's characteristics and associated symptoms. The economic and societal impact of migraines is substantial. It affects the sufferers' QOL and impairs work, social activities, and family life. There are many acute and preventive migraine treatments in the market. Acute treatment is either specific (triptans and ergots) or non-specific (analgesics). Disabling migraines should be treated with triptans. Increased headache frequency is an indication for preventive treatment. Preventive treatment decreases migraine frequency and improves QOL. More treatments are being developed, which provides hope to the many sufferers whose migraines are still uncontrolled.

Chronic Daily Headache

Chronic daily headache (CDH) refers to headache disorders experienced very frequently (15 or more days per month), including those associated with medication overuse (MOH). CDH can be divided into primary and secondary varieties.[93] Primary CDH is not related to a structural or systemic illness. Population-based studies in the United States, Europe, and Asia suggest that 4% to 5% of the general population has primary CDH,[94–96] and that 0.5% has severe headaches daily.[97,98] In population samples, chronic tension-type headache (CTTH) is the leading cause of primary CDH.[99] CDH patients account for the greatest number of consultations in headache subspecialty practices.[100] They often overuse medication, which may play a role in initiating or sustaining the pattern of pain. Anxiety, depression, and other psychological disturbances may accompany the headaches.[100]

Once secondary headache (including MOH) has been excluded, frequent headache sufferers are subdivided into two groups based on headache duration. When the headache duration is less than 4 h, the differential diagnosis includes cluster headache, paroxysmal hemicrania, idiopathic stabbing headache, hypnic headache, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT syndrome). When headache duration is longer than 4 h, the major primary disorders to consider are CM (see Box 38.4), hemicrania continua (HC), CTTH (Box 38.5), and new daily persistent headache (NDPH).[100] CM, NDPH, and HC are primary CDH disorders that are now included in the second IHS classification.[4] Transformed migraine (TM) is similar to CM.[4]

CM (see Box 38.4) has been called TM.[101] Most patients with this disorder are women, 90% of whom have a history of migraines without aura. Patients often report a transformation process characterized by headaches that become more frequent

• Box 38.5 Diagnostic Criteria for Tension-Type Headache

Infrequent Episodic Tension-Type Headache (IHS Diagnostic Criteria)

A. At least 10 episodes of headache occurring on <1 day/month on average (<12 days/year) and fulfilling criteria B-D
B. Lasting from 30 min to seven days
C. At least two of the following four characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. no nausea or vomiting
   2. no more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD

Frequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on one to 14 days/month on average for >3 months (≥12 and <180 days/year) and fulfilling criteria B-D
B. Lasting from 30 min to seven days
C. At least two of the following four characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. no nausea or vomiting
   2. no more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis[1]

Chronic Tension-Type Headache (IHS Diagnostic Criteria)

A. Headache occurring on ≥15 days/month on average for >3 months (≥180 days/year), fulfilling criteria B-D
B. Lasting hours to days, or unremitting
C. At least two of the following four characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. no more than one of photophobia, phonophobia, or mild nausea
   2. no moderate/severe nausea or vomiting
E. Not better accounted for by another ICHD-3 diagnosis

IHS, International Headache Society.

over months to years, with the associated symptoms of photophobia, phonophobia, and nausea becoming less severe and less frequent. A pattern of daily or nearly daily headaches often develops that phenomenologically resembles a mixture of tension-type headache (TTH) and migraine. That is, the pain is often mild to moderate and is not always associated with photophobia, phonophobia, or gastrointestinal features. Other characteristics of migraine, including aggravation by menstruation and other trigger factors, as well as unilaterality and gastrointestinal symptoms, may persist. Attacks of full-blown migraine superimposed on a background of less severe headaches occur in many patients. The term TM had been used to refer to this process. The term CM is now being used by the IHS, in part because a history of transformation is often missing.

Drug Overuse and Medication Overuse (Rebound) Headache (Box 38.6)

MOH was previously called rebound headache, drug-induced headache, and medication misuse headache. Patients with frequent headaches often overuse analgesics, opioids, ergotamine, and triptans. Although stopping the acute medication may result in the development of withdrawal symptoms and a period of increased headache, subsequent improvement in headache usually occurs.[102–106] Many primary CDH patients who were withdrawn from ergotamine and analgesics and given no further therapy no longer had daily headaches, although about 40% still had episodic migraine attacks.[96,107]

Definition and Classification of Medication Overuse Headache

In 1988 the IHS used the term "drug-induced headache" for MOH.[3] Overuse is now defined in terms of treatment days per month (see Box 38.6).

The epidemiology of MOH is uncertain. In European headache centers, 5% to 10% of patients have drug-induced headaches. One series of 3000 consecutive headache patients reported that 4.3% had drug-induced headaches.[108] Experience in the United Kingdom (P. Goadsby, personal communication) suggests that drug-associated headache is more common than the literature suggests. In American specialty headache clinics, as many as 80% of patients with primary CDH were reported to use analgesics on a daily or nearly daily basis.[96] Other headache clinics have reported a smaller percentage but a majority nonetheless.[109] In India, in contrast, medication overuse is less common.[110]

Diener and colleagues[111,112] summarized 29 studies that included 2612 patients with chronic MOH. Migraine was the primary headache in 65% of patients, TTH in 27%, and mixed or other headaches (i.e. cluster headache) in 8%. Women had more drug-induced headaches than men did (3.5:1; 1533 women, 442 men). This ratio is slightly higher than one would expect because of the usual gender differences in migraine frequency. The mean duration of primary headache was 20.4 years. The mean admitted time of frequent drug intake was 10.3 years in one study, and the mean duration of daily headache was 5.9 years. Results from headache diaries show that the number of tablets or suppositories taken daily averaged 4.9 (range, 0.25 to 25). Patients averaged 2.5 to 5.8 different pharmacologic components simultaneously (range, 1 to 14).[112]

• Box 38.6 Headache Attributed to Medication Overuse

A. Headache present on more than 15 days/month in a patient with a preexisting headache disorder
B. Regular overuse for more than three months of one or more acute or symptomatic treatment drugs as defined under subforms of 8.2.
   1. Ergotamine, triptans, opioids, *or* combination analgesic medications on 10 or more days/month regularly for more than three months
   2. Simple analgesics *or* any combination of ergotamine, triptans, analgesics, and opioids on 15 days/month or more regularly for more than three months without overuse of any single class alone
C. Not better accounted for by another ICHD-3 diagnosis

A prospective study of 98 patients investigated the pharmacologic features, such as the mean critical duration until the onset of MOH, mean critical monthly intake frequency, and mean critical monthly dosages, as well as the specific clinical features of MOH after the overuse of different acute headache drugs.[112] In this study, triptan overuse far outnumbered ergot overuse. This reflects the fact that despite the high cost, triptans have become widely used (and overused) and suggests that they are about to become the most important group causing MOH. Unlike patients who suffer from MOH following ergot or analgesic overuse, migraine patients (but not TTH patients) with triptan-induced headache did not describe the typical tension-type daily headache but rather a migraine-like daily headache (a unilateral, pulsating headache with autonomic disturbances) or a significant (and pure) increase in migraine attack frequency. Furthermore, the delay between frequent medication intake and the development of daily headache was the shortest with triptans (1.7 years), longer with ergots (2.7 years), and the longest with analgesics (4.8 years). Intake frequency (single dosages per month) was the lowest for triptans (18 single dosages per month), higher for ergots (37 single dosages per month), and the highest for analgesics (114 single dosages per month). Hence triptans cause a different spectrum of clinical features and result in MOH faster and with lower dosages than needed with other substance groups.[113]

In addition to exacerbating the headache disorder, drug overuse has other serious effects. Overuse of acute drugs may interfere with the effectiveness of preventive headache medications. Prolonged use of large amounts of medication may cause renal or hepatic toxicity in addition to tolerance, habituation, or dependence. Tolerance refers to decreased effectiveness of the same dose of an analgesic, which often leads to the use of higher doses to achieve the same degree of effectiveness. Habituation and dependence are, respectively, psychological and physical needs to repeatedly use drugs.

Epidemiology

In population-based surveys using the Silberstein-Lipton criteria, primary CDH was found to occur in 4.1% of Americans, 4.4% of Greeks, 3.9% of elderly Chinese, and 4.7% of Spaniards. Population-based estimates for the one year prevalence of CTTH are 1.7% in Ethiopia,[114] 3% in Denmark,[115] 2.2% in Spain,[116] 2.7% in China,[98] and 2.2% in the United States.[97]

Scher and coworkers,[97] using a validated computer-assisted telephone interview, ascertained the prevalence of CDH in 13,343 individuals aged 18 to 65 years in Baltimore County, Maryland. Those reporting 180 or more headaches per year were classified as having frequent headaches. Three mutually exclusive subtypes of frequent headache were identified: TM, CTTH, and unclassified frequent headache. The overall prevalence of CDH was 4.1% (5.0% in women, 2.8% in men; 1.8:1 female-to-male ratio). The prevalence was the highest in the lowest educational category for both men and women. More than half (52% of women, 56% of men) met the criteria for CTTH (2.2%), almost a third (33% of women, 25% of men) met the criteria for TM (1.3%), and the remainder (15% of women, 19% of men) were unclassified (0.6%). Overall, 30% of women and 25% of men who were frequent headache sufferers met the IHS criteria for migraine (with or without aura). Based on chance, migraine and CTTH would co-occur in 0.22% of the population; the fact that TM occurred in 1.3% of this population would suggest that their co-occurrence is more than random.

Castillo and associates[116] sampled 2252 subjects older than 14 years in Cantalucia, Spain. Overall, 4.7% had CDH. According to the criteria of Silberstein and colleagues,[100] none had HC, 0.1% had NDPH, 2.2% had CTTH, and 2.4% had TM. Nineteen percent of CTTH patients and 31.1% of TM patients had a history of acute medication overuse. Eight patients had a history of migraines without aura and now had primary CDH with the characteristics of TTH only. These headaches met the criteria for CM but could have been migraines and coincidental CTTH.

Wang and associates[98] looked at the characteristics of primary CDH in a population of elderly Chinese individuals (older than 65 years) in two townships in Kinmen Island. Seventy-seven percent of the eligible population (1533 of 2003) participated. Sixty patients (3.9%) had CDH. Significantly more women than men had primary CDH (5.6% and 1.8%, $P < 0.001$). Of the patients with primary CDH, 42 (70%) had CTTH (2.7%), 15 (25%) had CM (1%), and 3 (5%) had other CDH. Only 23% of patients had consulted a physician for headaches in the previous year.

Lu and colleagues[117] conducted a two-stage population-based headache survey of subjects 15 years or older in Taipei, Taiwan. Subjects who had experienced CDH in the past year were identified, interviewed, and followed up. CDH was defined as a headache frequency of greater than 15 days a month with a duration of more than 4 h per day. Of the 3377 participants, 108 (3.2%) fulfilled the criteria for CDH, with a higher prevalence in women (4.3%) than in men (1.9%). TM was the most common subtype (55%), followed by CTTH (44%). Thirty-four percent of the CDH subjects overused analgesics.

The gradual evolution of the definition of CM has resulted in varying conclusions drawn from prevalence studies. Two reviews that defined chronic headache as being present on 15 or more days per month estimated its global prevalence to be 3% to 4%.[118,119] A systematic review from 2010 focused on 12 worldwide, population-based incidence and prevalence studies that determined the rates of CM with either the Silberstein-Lipton criteria for TM[101,120,121] or the current ICHD-2R criteria for CM.[122] The prevalence of CM in these studies ranged from 0.0% to 5.1% (initial estimates of these rates were typically in the range of 1.4% to 2.2%) and varied by WHO-defined geographic regions, as well as by gender.[122] These estimates are imperfect because of the heterogeneity of definitions applied across studies and the lack of data from certain regions. Nevertheless, the target population is equally well defined by both the Silberstein-Lipton TM criteria and the ICHD-2R term CM; thus the data presented are likely to give a reasonably accurate global perspective. The prevalence of CM in this systematic review also suggests that this condition represents approximately half of all cases of chronic primary headache. In further population-based studies—HUNT 2 and HUNT 3, published in 2011—the age-adjusted prevalence of CM was consistently 0.5% throughout an 11 year follow-up period.[123]

Risk Factors (Box 38.7)

Wang and associates[98] ascertained that significant risk factors for CDH included analgesic overuse (odds ratio [OR] = 79), a history of migraine (OR = 6.6), and a Geriatric Depression Scale-Short Form score of eight or higher (OR = 2.6). At follow up, patients with persistent primary CDH had a significantly higher frequency of analgesic overuse (33% vs. 0%, $P = 0.03$) and major depression (38% vs. 0%, $P = 0.04$).

Granella and colleagues[124] found that risk factors associated with the evolution of migraine without aura into TM included head

• Box 38.7 Risk Factors for Chronic Daily Headache

High headache frequency
Female gender
Obesity (body mass index >30)
Snoring
Stressful life events
High caffeine consumption
Acute medication overuse
Depression
Head trauma
History of migraine
Less than a high school education

trauma (OR = 3.3), analgesic use with every attack (OR = 2.8), and long duration of oral contraceptive use.

Scher and coworkers[125] described factors that predict CDH onset and remission in an adult population. CDH was more common in women (OR = 1.65 [1.3 to 2.0]), those previously married (OR = 1.5 [1.2 to 1.9]), those with obesity (body mass index >30) (OR = 1.27 [1.0 to 1.7]), and those with less education. Obesity, high baseline headache frequency, high caffeine consumption, habitual daily snoring, and stressful life events were significantly associated with new-onset CDH.[126] Having less than a high school education was associated with a threefold increased risk for CDH (OR = 3.56 [2.3 to 5.6]).

Bigal and colleagues,[127] in a clinic-based study, looked for risk factors associated with CDH and its subtypes. TM without MOH (vs. episodic migraine) was associated with allergies, asthma, hypothyroidism, hypertension, and daily caffeine consumption.

Zwart and associates[128] examined the relationship between analgesic use at baseline and the subsequent risk for chronic pain (≥15 days/month) and analgesic overuse in a population-based study. In total, 32,067 adults reported the use of analgesics from 1984 to 1986 and at the follow up 11 years later (1995 to 1997). The risk ratios for chronic pain and analgesic overuse in the different diagnostic groups (i.e. migraine, nonmigrainous headache, and neck pain) were estimated in relation to analgesic consumption at baseline. Individuals who reported using analgesics daily or weekly at baseline had a significantly increased risk of having chronic pain at follow up. The risk was most evident for CM (relative risk [RR] = 13.3, 95% CI = 9.3 to 19.1), intermediate for chronic nonmigrainous headaches (RR = 6.2, 95% CI = 5.0 to 7.7), and lowest for chronic neck pain (RR = 2.4, 95% CI = 2.0 to 2.8). In subjects with chronic pain associated with analgesic overuse, the RR was 37.6 (95% CI = 21.3 to 66.4) for CM, 14.4 (95% CI = 10.4 to 19.9) for chronic nonmigrainous headaches, and 7.1 for chronic neck pain (95% CI = 5.5 to 9.2). The RR for chronic headache (migraine and nonmigrainous headache combined) associated with analgesic overuse was 19.6 (95% CI = 14.8 to 25.9) versus 3.1 (95% CI = 2.4 to 4.2) for those without overuse. Analgesic overuse strongly predicts chronic pain and chronic pain associated with analgesic overuse 11 years later, especially in those with CM.

Although data on the natural history of patients with CM are not available (because of the 10 to 15 year time scale that would be required for a population-based study of this condition), information from the American migraine prevalence and prevention (AMPP) on the clinical evolution of this condition was published in 2011.[129] Longitudinal data over a three year period were analyzed to determine rates of CM remission and to assess predictors of remission via logistic regression models. Three hundred and eighty-three individuals who had CM in 2005 were identified and evaluated in 2006 and 2007. Among individuals with CM at baseline, 52.7% continued to report this condition for at least one year of follow up. The study also found that 34% had persistent CM (defined as CM across all three years), whereas only 26% had remission of CM (defined as fewer than 10 headache days per month).[129] Over a two year period, the individuals with persistent CM demonstrated increased disability, whereas those with remission showed decreased disability. Predictors of remission included a lower baseline headache frequency (15 to 19 headache days per month vs. 25 to 31 headache days per month; OR = 0.29, 95% CI = 0.11 to 0.75) and the absence of allodynia (OR = 0.45, 95% CI = 0.23 to 0.89).

Treatment

Overview

Patients with CDH can be challenging to treat, especially when the disorder is complicated by medication overuse, comorbid psychiatric disease, low tolerance of frustration, and physical and emotional dependency.[95,130] We recommend the following steps. First, exclude secondary headache disorders. Second, diagnose the specific primary headache disorder (CM, CTTH, HC, or NDPH). Third, identify comorbid medical and psychiatric conditions and exacerbating factors, especially medication overuse. Limit acute medications (with the possible exception of long-acting NSAIDs). Patients should start taking preventive medication (to decrease reliance on acute medication), with the explicit understanding that the drugs may not become fully effective until medication overuse has been eliminated.[51] Some patients need to have their headache cycle terminated.[51] Patients need education and continuous support during this process. Outpatient detoxification options, including outpatient infusion in an ambulatory infusion unit, are available. If outpatient treatment proves difficult or is dangerous, hospitalization may be required.[93,131]

Two separate studies in Europe and the United States showed that topiramate at a dose of 100 mg daily was effective as preventive therapy for CM.[132,133] The key difference between the two studies was that patients were allowed to take acute rescue medication as usual in the European trial[132] but not in the United States trial.[133] Remarkably, the benefits of topiramate extended to the subgroup of patients who were overusing acute medications, as demonstrated by the significant reductions in mean monthly migraine days in this group versus the placebo group.

The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT 1 and 2) multicenter randomized clinical trials were conducted to evaluate the efficacy and safety of botulinum toxin type A as prophylactic treatment in adults with CM. A total of 1384 patients with CM were enrolled across trials.[134–136] Patients were stratified into groups according to whether they were overusing acute headache medications at baseline and were randomly assigned in a 1:1 ratio to treatment with either botulinum toxin type A or placebo injections. A total dose of 155 units of botulinum toxin type A was administered to 31 sites in seven head and neck muscles.[134–136] The PREEMPT study results demonstrated significant improvement at the population level in multiple measures of headache symptoms and improvement in patients' functioning, vitality, psychological distress, and overall health-related QOL in response to treatment with botulinum toxin type A.

The four anti-CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, galcanezumab) are safe, effective, and

approved for the prevention of episodic migraine and CM even in the presence of MOH without acute medication withdrawal.

In some cases, CDH reverts to episodic headaches when preventive medication is initiated and acute medications are limited. In other cases, only moderate or no improvement may occur. Zeeberg and coworkers[137] described the treatment outcomes of patients withdrawn from medication overuse. They studied 337 outpatients in whom MOH was diagnosed and who were treated and discharged from the Danish Headache Centre in 2002 and 2003. A 46% decrease in headache frequency from the first visit to dismissal was noted ($P < 0.0001$). Patients with no improvement two months after complete drug withdrawal ($n = 88$) subsequently responded to pharmacologic or nonpharmacologic prophylaxis (or both) with a 26% decrease in headache frequency as measured from the end of withdrawal to dismissal. At dismissal, 47% of patients were being maintained on prophylaxis. In this population, about half of the MOH patients benefited from drug withdrawal alone.[137]

Prognosis

The AMPPS was published in 2011.[129] Among individuals with CM at baseline, 52.7% continued to report this condition for at least one year of follow up. The study also found that 34% had persistent CM (defined as CM across all three years), whereas only 26% had remission of CM (defined as fewer than 10 headache days per month).[138] Over two years, the individuals with persistent CM demonstrated increased disability, whereas those with remission showed decreased disability. Predictors of remission included a lower baseline headache frequency (15 to 19 headache days per month vs. 25 to 31 headache days per month; OR = 0.29, 95% CI = 0.11 to 0.75) and the absence of allodynia (OR = 0.45, 95% CI = 0.23 to 0.89). In addition, retrospective analysis suggests that there may be periods of stable drug consumption and periods of accelerated medication use. Patients treated aggressively generally improve. There are no literature reports of spontaneous improvement of rebound headache, although this may happen. We performed follow-up evaluations on 50 hospitalized primary CDH drug overuse patients who were treated with repetitive intravenous DHE and became headache free.[139] Once detoxified, treated, and discharged, most patients did not resume daily analgesic or ergotamine use. Seventy-two percent continued to show significant improvement at three months, and 87% continued to show significant improvement after two years. This would suggest at least 70% improvement at two years in the initial group (35 of 50) if allowance is made for patients lost to follow up.

Our two year success rate of 87% is consistent with the long-term success rates reported in the literature.[139] In a series of 22 papers published between 1975 and 1999, the success rate of withdrawal therapy (often accompanied by pharmacologic or behavioral intervention, or both) for patients overusing analgesics, ergotamine, or both was between 48% and 91%, with the rate being reported as 77% or higher in ten papers.[103,104,107,124,140–145]

Tension-Type Headache

Epidemiologic studies of the general population have shown that TTH is the most common type of headache, with a lifetime prevalence of 69% in men and 88% in women.[146] TTHs can begin at any age, but onset during adolescence or young adulthood is most common. The prognosis of patients with frequent episodic TTH (ETTH) and CTTH was favorable in a Danish follow up to a cross-sectional headache study that included 549 persons. Among 146 subjects with frequent ETTH and 15 with CTTH at baseline, 45% experienced infrequent or no TTH (remission), 39% had frequent ETTH, and 16% experienced CTTH (poor outcome) at follow up. A poor outcome was associated with baseline CTTH, coexisting migraine, sleeping problems, and single state.[147]

Clinical Features and Associated Disorders (see Box 38.5)

ETTH is now classified as either infrequent (<1 day/month or 12 days/year) or frequent (>1 but <15 days/month or >12 but <180 days/year). The IHS criteria for TTH require that patients experience at least 10 previous headaches, each lasting 30 min to seven days (median, 12 h) and with at least two of the following characteristics: a pressing or tightening (non-pulsating) quality, mild to moderate intensity, bilateral location, and no aggravation with physical activity. In addition, the patient should not have nausea or vomiting or a combination of photophobia and phonophobia. ETTH occurs less than 15 days per month, whereas CTTH occurs 15 or more days per month.[148] The pain is a dull, achy, nonpulsatile feeling of tightness, pressure, or constriction (vise-like or hatband-like), and it is usually mild to moderate, in contrast to the moderate to severe pain of migraine. The intensity increases with headache attack frequency.[149] Most patients have bilateral pain, but the location varies considerably within and between patients and can involve the frontal, temporal, occipital, or parietal regions, alone or in combination, and can change locations during an attack.[150] An occipital location is less common than a frontal or temporal location. Some patients have neck or jaw discomfort or have frank problems with their temporomandibular joint.[151,152]

The onset of TTH is gradual, often occurring after or during stress, and the pain is typically worse late in the day. There is no prodrome. The pain is usually a nagging, tight, or vise-like bilateral pressure that is located in the forehead, the temples, or the back of the head. It may radiate to the neck and shoulders. There are no associated autonomic or gastrointestinal symptoms except for occasional anorexia. The frequency of ETTH ranges from two to 12 days per month, with a median of six days per month. The headaches may be associated with menstruation.[148,153]

Twenty-five percent of TTH patients also have migraines.[154] What we call ETTH may be two distinct disorders. The first disorder may be a mild migraine. The second may be pure TTH that is not associated with other features of migraine (nausea, photophobia, or sensitivity to movement) or with attacks of severe migraine.[4] The fact that sumatriptan is effective for the TTH that migraineurs experience but not for the TTH that non-migraineurs experience supports this concept.[155]

Patients with ETTH are no different from controls in terms of stress, depression, anxiety, emotional conflicts, sleeping problems, and fatigue. Patients with CTTH are often depressed.[153]

Differential Diagnosis

Migraine is the headache disorder most frequently confused with TTH. Both can be bilateral, non-throbbing, and associated with anorexia. Migraine is more severe, often unilateral, and frequently associated with nausea. Idiopathic intracranial hypertension, brain tumor headache, chronic sphenoid sinusitis, and cervical, ocular, and temporomandibular disorders need to be considered.[148,153]

Evaluation

Most patients with a long history of unchanged ETTH do not require extensive evaluation if they have normal findings on neurologic examination and are otherwise healthy. Patients with CTTH should be evaluated with CT or MRI, even if the results of the general and neurologic examination are normal. A metabolic screen, complete blood count, electrolytes, and kidney and thyroid function studies are also appropriate.[153]

Management

TTH patients usually self-medicate with over-the-counter analgesics (aspirin, acetaminophen, NSAIDs), with or without caffeine. If these medications are not effective, prescription NSAIDs or combination analgesic preparations can be used. Narcotics and combination analgesics that contain sedatives or caffeine should be limited because overuse may cause dependence. Symptomatic medication overuse can cause ETTH to convert to CTTH. Patients with both migraine and TTH benefit from specific migraine medication, such as sumatriptan or DHE (see Boxes 38.5 and 38.6).[148,153]

Preventive therapy should be administered when a patient has frequent headaches that produce disability or may lead to symptomatic medication overuse. Medications used for the prevention of TTH include anti-depressants, β-blockers, and anti-convulsants. Anti-depressants, the medication of first choice, should be started at a low dose and increased slowly every three to seven days. An adequate trial period of at least one to two months must be allowed. The addition of biofeedback therapy or β-blocking agents may improve its therapeutic benefit.[148,153]

Prognosis and Future Perspectives

ETTH is a benign recurrent condition that usually improves with time. However, some patients progress to CTTH, especially when analgesic overuse is present. The prognosis of patients with CTTH is controversial because many studies include patients with more severe headaches and coexisting conditions, such as migraine and psychiatric disorders.

Cluster Headache and Other Trigeminal Autonomic Cephalgia (Box 38.8)

The short-lasting primary headache syndromes may be conveniently divided into those that exhibit marked autonomic activation and those without autonomic activation. This group includes cluster headache (episodic or chronic), paroxysmal hemicrania (episodic or chronic), and SUNCT syndrome.

Pathogenesis and Pathophysiology

The pathogenesis of cluster headache involves the trigeminovascular system, as demonstrated by a marked increase in the level of CGRP in the cranial venous circulation during attacks.[156] Activation of the parasympathetic system has been corroborated by the finding of dramatically elevated levels of vasoactive intestinal polypeptide during attacks[156] with robust ipsilateral autonomic features. Cluster events are probably related to alterations in the circadian pacemaker, which may be because of hypothalamic dysfunction. Attacks increase following the beginning and end of daylight saving time, and there is a loss of the circadian rhythm for blood pressure, temperature, and hormones, including prolactin, melatonin, cortisol, and β-endorphins. Evidence for the role of the hypothalamus in the pathogenesis of cluster headaches has come from functional and morphometric neuroimaging. May and colleagues demonstrated marked activation in the ipsilateral ventral hypothalamic gray matter during nitroglycerin-induced acute cluster headache attacks using positron emission tomography.[157] Neurogenic inflammation, dysfunction of the carotid body chemoreceptor, an imbalance in central parasympathetic and

• Box 38.8 Cluster Headache

A. At least five attacks fulfilling criteria B to D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 min f untreated
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhea
      c) eyelid edema
      d) forehead and facial sweating
      e) miosis and/or ptosis
   2. a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day
E. Not better accounted for by another ICHD-3 diagnosis

Episodic Cluster Headache

A. Attacks fulfilling the above criteria A to E for *Cluster Headache*
B. At least two cluster periods lasting seven to 365 days and separated by pain-free remission periods of three months or longer

Chronic Cluster Headache

A. Attacks fulfilling criteria A to E for *Cluster Headache*
B. Attacks recurring longer than one year without remission periods or with remission periods lasting less than three months for at least one year

Paroxysmal Hemicrania

A. At least 20 attacks fulfilling criteria B to F
B. Attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 2 to 30 min
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhea
      c) eyelid edema
      d) forehead and facial sweating
      e) miosis and/or ptosis
   2. a sense of restlessness or agitation
D. Occurring with a frequency of >5 per day[1]
E. Prevented absolutely by therapeutic doses of indomethacin[2]
F. Not better accounted for by another ICHD-3 diagnosis.

Episodic Paroxysmal Hemicrania

A. Attacks fulfilling criteria A to F for *Paroxysmal Hemicrania*
B. At least two attack periods lasting seven to 365 days and separated by pain-free remission periods of three months or longer

Chronic Paroxysmal Hemicrania

A. Attacks fulfilling criteria A to F for *Paroxysmal Hemicrania*
B. Attacks recurring more than one year without remission periods or with remission periods lasting less than three months

sympathetic tone, and increased responsiveness to histamine have been proposed as the cause of cluster headache.[158]

Epidemiology and Risk Factors

With an incidence of 0.01% to 1.5% in various populations, the prevalence of cluster headaches is lower than that of migraine or TTH. Men have a higher prevalence than women, and African American patients have a higher prevalence than Caucasian patients. Recent evidence suggests a progressively decreasing male preponderance: the male-to-female ratio based on the year of onset in Manzoni's study[159] decreased from 6.2:1 in the 1960s to 2.1:1 in the 1990s.[160] A family history of cluster headache is rare. The most common form of cluster headache is an episodic cluster. The rarest form is chronic cluster headache without remissions, with only about 1% of patients suffering from this variety of cluster. Cluster headaches can begin at any age but generally commence in the late twenties. Cluster headaches rarely begin in childhood and develop in only about 10% of patients when they are in their sixties.[158,161]

Clinical Features and Associated Disorders

A. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 min if untreated
B. Either or both of the following:

Patients with cluster headaches have multiple episodes of short-lived but severe, unilateral orbital, supraorbital, or temporal pain lasting 15 to 180 min if untreated, with either or both of the following: 1) at least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis or 2) a sense of restlessness or agitation.

An episodic cluster consists of headache periods of one week to one year, with remission periods lasting at least 14 days, whereas a chronic cluster headache has either no remission periods or remissions that last less than 14 days.[158,161]

The pain of a cluster attack increases to excruciating levels rapidly (within 15 min). The attacks often occur at the same time each day and frequently awaken patients from sleep. If the condition is left untreated, the attacks usually last from 30 to 90 min, but they may last as long as 180 min. The pain is deep, constant, boring, piercing, or burning in nature and located in, behind, or around the eye. It may radiate to the forehead, temples, jaws, nostrils, ears, neck, or shoulders. During an attack, patients often feel agitated or restless and feel a need to isolate themselves and move around. Gastrointestinal symptoms are uncommon. A small subset of patients experience a typical migraine aura before a cluster headache attack.[162] Attack frequency varies from one every other day to eight per day, with cluster periods lasting a week to a year. Remissions between cluster periods generally last from six months to two years. Most patients have one or two cluster periods per year that last two to three months, with one to two attacks per day.[158]

Peptic ulcer disease is the only known associated medical disorder. Secondary cluster-like headaches may be because of structural lesions near the cavernous sinuses.[158,161]

Differential Diagnosis

The differential diagnosis of cluster headache includes chronic paroxysmal hemicrania, migraine, trigeminal neuralgia, temporal arteritis, pheochromocytoma, Raeder's paratrigeminal syndrome, Tolosa-Hunt syndrome, sinusitis, and glaucoma.[158] Raeder's syndrome has characteristics similar to cluster headaches. It may be associated with severe pain, unilateral and supraorbital distribution, and an associated partial Horner syndrome. It is distinct from cluster headache in that there are no distinct attacks, and the pain is constant.

Evaluation

No studies have addressed the need for testing in patients with cluster-like headaches. In most cases, a careful history is all that is needed to make the diagnosis. MRI of the head is justified only for atypical cases or those with abnormal findings on neurologic examination (except when the abnormality is Horner's syndrome).

Management

Patients with cluster headaches should avoid alcohol and nitroglycerin, but other dietary and drug restrictions have little effect. Pharmacologic treatment of cluster headaches is divided into acute and preventive therapy, and recommendations are based mainly on uncontrolled trials.[158,161] Because oral preparations are absorbed slowly, they are not recommended for acute attacks. Effective acute treatments that provide a rapid onset of action include oxygen, sumatriptan, DHE, and (perhaps) topical local anesthetics. Inhaled oxygen, 7 to 10 L/min for 10 min following the onset of the headache, is 70% effective and is often the first choice of treatment. Parenteral injections of sumatriptan or DHE provide significant relief to about 80% of patients. An intranasal local anesthetic provides relief for some patients.[158,161]

Most patients with cluster headaches require preventive treatment because each attack is too short in duration and too severe in intensity to treat with only acute medication. In addition, ergotamine, DHE, sumatriptan, and oxygen may just postpone rather than abort the attack. Preventive therapy for cluster headache includes ergotamine, calcium channel blockers, lithium, corticosteroids, divalproex, topiramate, melatonin, and galcanezumab for an episodic cluster. Occasionally, indomethacin is effective. If medical therapy fails, surgical intervention may be beneficial for psychologically stable patients with strictly unilateral chronic cluster headaches. The surgery consists of neuronal ablative procedures directed toward the sensory input of the trigeminal nerve and autonomic pathways and is effective in 75% of patients.[163] Gamma knife radiosurgery was reported to be effective in six medically recalcitrant cluster headache patients, but delayed radiation necrosis can occur.[164] Deep brain (hypothalamic) stimulation has been reported to be effective for intractable chronic cluster headaches.[165] Since cluster headache is a chronic headache disorder that may last a patient's lifetime, the prognosis is guarded. Drug therapy may help convert chronic headaches in some patients to episodic cluster headaches.[158]

Deep brain stimulation of the posterior hypothalamus (hDBS) and ONS along the greater occipital nerve have been introduced, and evidence is accumulating. Deep brain stimulation was developed based on findings of activation in the posterior part of the lateral portion of the hypothalamus.[166] Both hDBS and ONS have so far resulted in positive outcomes in patients with drug-resistant chronic cluster headache (about a 50% reduction in attacks), but long-term studies have revealed that a positive outcome, especially with ONS, may take a week to months of stimulation to be reached, thus pointing at long-term brain alterations in pain processing as a mechanism.[167–170] With both hDBS and ONS, the

pain and autonomic symptoms return to baseline levels when the stimulator is turned off.[167–170] So far, no predictors of treatment response have been found, and greater occipital nerve block does not predict ONS response.[171]

Sphenopalatine Ganglion Stimulation

In 2010 Ansarinia and coauthors described the acute effect of external electrical stimulation in eight patients with cluster headache, of whom four achieved complete freedom from pain, three achieved a reduction in pain, and one had no change.[172] More sophisticated systems have been developed, and an ongoing European multicenter study is now testing the effect of an electrode implanted directly in the sphenopalatine fossa very close to the sphenopalatine ganglion (SPG). The preliminary results are very promising; there appears to be a significant preventive effect in addition to an acute abortive effect. The side effects have been limited; therefore the therapy looks promising for severely affected chronic cluster headache patients. However, long-term studies are needed. Furthermore, important insight into the pathophysiology of cluster headaches and the mechanisms of SPG stimulation can be achieved.

Chronic Paroxysmal Hemicrania (see Box 38.8)

Chronic paroxysmal hemicrania resembles cluster headache in character but is distinguished by its dramatic responsiveness to indomethacin therapy. The pathophysiology of chronic paroxysmal hemicrania is unknown. The changes in intraocular pressure that occur during attacks suggest autonomic dysfunction, and the periodicity of this disorder suggests a central generator.[173] In contrast to cluster headache, chronic paroxysmal hemicrania is a rare disorder that affects women more than men (ratio of approximately 7:1). Its prevalence is approximately 2% that of cluster headache.[173]

Like patients with cluster headaches, those with chronic paroxysmal hemicrania have severe unilateral headaches associated with unilateral nasal stuffiness, lacrimation, conjunctival eye tearing, ptosis, and eyelid edema. Headaches average 13 min in duration and occur an average of 11 times per day. Occasionally, patients experience a continuous dull ache between attacks. Ten percent of patients can trigger attacks by flexing, rotating, or pressing the upper portion of the neck.[173] Typically, no remissions occur. Rarely, a patient has episodic paroxysmal hemicrania with remissions that last weeks or months. Patients may evolve from the episodic to the chronic form of the illness. By definition, chronic and episodic hemicranias are responsive to indomethacin. No other medical or psychiatric disorders have been associated with chronic paroxysmal hemicrania.[173]

Differential Diagnosis

The differential diagnosis of chronic paroxysmal hemicrania is similar to that for cluster headaches. In addition, patients with "jabs and jolts syndrome" occasionally resemble those with chronic paroxysmal hemicrania. A rare headache disorder called SUNCT syndrome should be considered, although these headaches are much shorter in duration (15 to 30 s) and occur much more frequently (many times per hour) than those of chronic paroxysmal hemicrania.

Evaluation

When evaluating a patient with chronic paroxysmal hemicrania, a trial of indomethacin is necessary to establish the diagnosis. Brain imaging with MRI or CT should be undertaken to exclude symptomatic causes of apparent chronic paroxysmal hemicrania. The treatment of choice is indomethacin (in a dose of up to 200 mg/day). Aspirin may also be beneficial, but it does not usually afford complete relief. Chronic paroxysmal hemicrania may last indefinitely, but the indomethacin requirement may be reduced over time. Temporary remissions and spontaneous cures have been described. Selective prostaglandin synthesis inhibitors, or indomethacin-like drugs without the gastrointestinal side effects of the current NSAIDs, are in development and may be beneficial.

Summary

Headache is a problem that has plagued humans since the beginning of recorded time. Headaches can severely interfere with daily functioning and productivity. Migraine is a chronic neurologic disease characterized by episodic attacks of headache and associated symptoms. The migraine attack can consist of premonitory, aura, headache, and resolution phases. The IHS subdivides migraine into migraine with aura and migraine without aura. Migraine varies widely in its frequency, severity, and impact on patients' QOL. Pharmacologic treatment of migraine may be acute (abortive) or preventive (prophylactic), and patients with frequent, severe headaches often require both approaches. CDH refers to headache disorders experienced very frequently (15 or more days per month), including headaches associated with medication overuse. The major primary disorders to consider are CM, HC, CTTH, and NDPH. MOH was previously called rebound headache, drug-induced headache, and medication misuse headache. Patients with frequent headaches often overuse analgesics, opioids, ergotamine, and triptans. Patients with CDH can be difficult to treat. First, secondary headache disorders should be excluded; second, the specific primary headache disorder should be diagnosed; and third, comorbid medical and psychiatric conditions should be identified. Acute medications should be limited. Patients should start taking preventive medication, with the explicit understanding that the drugs may not become fully effective until medication overuse has been eliminated. TTH is the most common type of headache, with a lifetime prevalence of 69% in men and 88% in women. ETTH is now classified as either infrequent (<1 day/month or 12 days/year) or frequent (>1 but <15 days/month or >12 but <180 days/year). Patients with TTH usually self-medicate with over-the-counter analgesics, with or without caffeine. Preventive therapy should be administered when a patient has frequent headaches that produce disability or may lead to symptomatic medication overuse. Cluster headache and other trigeminal cephalgias are short-lasting primary headache syndromes that may be conveniently divided into those that exhibit marked autonomic activation and those without autonomic activation. This group includes cluster headache, paroxysmal hemicrania, and SUNCT syndrome. Patients with cluster headaches have multiple short-lived but severe unilateral, orbital, supraorbital, or temporal pain episodes. Chronic paroxysmal hemicrania resembles cluster headache in character but is distinguished by its dramatic responsiveness to indomethacin therapy.

Key Points

- Headaches are one of the most common reasons patients see their doctors, and besides the pain involved, they can severely interfere with daily functioning, QOL, and productivity.
- WHO ranks migraine among the world's most disabling medical illnesses, and approximately 28 million Americans have severe, disabling migraine headaches.
- Migraine attacks can consist of premonitory, aura, headache, and resolution phases. Premonitory symptoms occur in 20% to 60% of migraineurs, hours to days before the onset of the headache. They may include psychological, neurologic, constitutional, or autonomic features, such as depression, cognitive dysfunction, and bouts of food craving.
- There are many acute and preventive migraine treatments in the market. Acute treatment is either specific (triptans and ergots) or non-specific (analgesics). Preventive treatment decreases migraine frequency and improves QOL.
- CDH refers to headache disorders experienced very frequently (15 or more days per month), including those associated with medication overuse (MOH).
- Patients with frequent headaches often overuse analgesics, opioids, ergotamine, and triptans. Although stopping the acute medication may result in the development of withdrawal symptoms and a period of increased headache, subsequent improvement in headache usually occurs.
- ETTH is a benign recurrent condition that usually improves with time. However, some patients progress to CTTH, especially when analgesic overuse is present.
- Patients with cluster headaches have multiple episodes of short-lived but severe, unilateral orbital, supraorbital, or temporal pain with conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis; or a sense of restlessness or agitation.
- Most patients with cluster headaches require preventive treatment, which can include ergotamine, calcium channel blockers, lithium, corticosteroids, divalproex, topiramate, melatonin, and galcanezumab.
- If medical therapy fails completely for cluster headache, surgical intervention consisting of neuronal ablative procedures directed toward the sensory input of the trigeminal nerve and autonomic pathways may be considered and is effective in 75% of patients.

Suggested Readings

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39

Cervicogenic Headache, Post-meningeal Puncture Headache, and Spontaneous Intracranial Hypotension

LORI-ANN EDWARDS, LOUISE HILLEN, DEEPTI AGARWAL, DOST KHAN, REDA TOLBA

CERVICOGENIC HEADACHE

Definition

The International Headache Society (IHS) defines cervicogenic headache as "Headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain."[1]

Epidemiology

The incidence of cervicogenic headache is 2% when using the IHS criteria[2] and up to 4% when using the Cervicogenic Headache International Study Group (CHISG) criteria.[3] Furthermore, in studies conducted using the CHISG criteria for diagnosis, cervicogenic headaches were 66% more common in women.[4] It encompasses 17.7% of all severe headaches. Epidemiologic studies are limited because of the wide variation in the diagnostic criteria. Cervicogenic headaches represent 25% of headache cases seen in pain management clinics.

Pathophysiology

The pathogenesis of cervicogenic headaches can be explained by the overlap between the first three cervical nerves, the trigeminal nucleus, and the cervical plexus. This is illustrated in Fig. 39.1. The first three cervical nerves supply other structures, such as the upper cervical synovial joints and muscles, the dura mater of the upper spinal cord and posterior cranial fossa, and the intervertebral discs.[5] The nociceptive afferents from the first three cervical nerves overlap with the second-order neurons that also receive afferents from the trigeminal nerve through the trigeminal nerve spinal tract. This overlap occurs in the trigeminocervical nucleus and allows for referral of cervical pain to the occipital and auricular regions as well as frontal, parietal, and orbital regions because of trigeminal afferents.[6] The trapezius, sternocleidomastoid, and splenius capitis are also innervated by the cervical nerves, and trigger points within these muscles can cause cervicogenic headaches.[7] This is because nociceptive afferents from these muscles also converge with the trigeminocervical nucleus.[4]

Summary of Cervical Nerve Anatomy[5]

First Cervical Nerve
Second Cervical Nerve
Third Cervical Nerve

Diagnostic Criteria

Cervicogenic headaches can be diagnosed based on clinical symptoms that meet the criteria or diagnostic block.

A. Clinical Diagnosis

Table 39.1 describes the clinical criteria put forth by the CHISG for the diagnosis of cervicogenic headache.[8] In Table 39.2, the IHS International Classification of Headache Disorders 3 diagnostic criteria are described.[9]

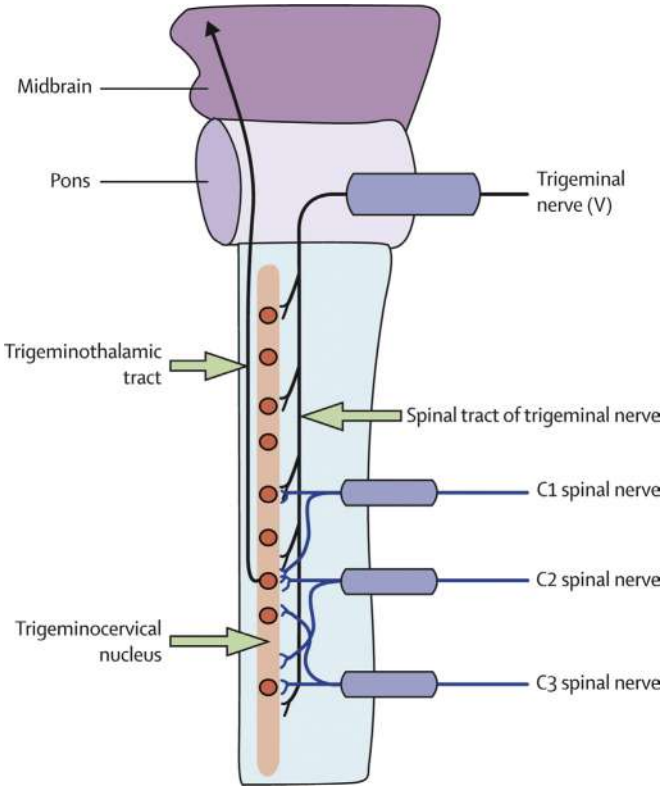
B. Diagnostic Block

While clinical diagnostic criteria help diagnose cervicogenic headaches, a true diagnostic block can completely relieve headaches. It can be used to confirm the diagnosis of cervicogenic headache, rather than relying on clinical diagnosis alone. The third occipital nerve block can be used to diagnose pain arising from C2–C3 zygapophysial joint disease and is performed under fluoroscopic guidance. Patients who obtain complete relief of their headache after controlled blocks of the third occipital nerve can be treated successfully by radiofrequency neurotomy of the nerve.[10]

Diagnostic medial branch block (MBB) of C3 and C4 can also be performed together with a third occipital nerve block to help with the associated component of neck pain. The techniques for C3 and C4 MBB and third occipital nerve block are described in detail under interventional management of cervicogenic headache.[10]

Differential Diagnosis

Serious conditions should be ruled out in the presence of alarming features or red flags. Red flags include fever and chills, age >50 years, history of cancer, night pain leading to awakening, and weight loss. Special attention should be paid to high-risk patients, such as immunocompromised individuals, as they are more susceptible to more serious conditions, such as infections. The differential diagnosis includes:



• **Figure 39.1** Nociceptive afferents of the trigeminal and upper three cervical spinal nerves converge onto second-order neurons in the trigeminocervical nucleus in the upper cervical spinal cord. This convergence mediates the referral of pain signals from the neck to regions of the head innervated by cervical nerves or the trigeminal nerve. (Reprinted with permission from Elsevier. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. *Lancet Neurol* 2009;8:959–968.)

Internal Carotid or Vertebral Artery Dissection

- The vertebral and internal carotid arteries are innervated by the cervical nerves, and dissection of these vessels can result in headaches.[7]
- May have stroke-like symptoms within one to three weeks.[6]
- Treatment with cervical manipulation can be fatal.[6]

Tumor in the Posterior Fossa, Arnold Chiari Formation

- The dura mater in the posterior cranial fossa is supplied by the sinuvertebral nerves C1–3[5].

Herniated Cervical Vertebral Disc

- The C3 vertebral branch supplies the intervertebral discs of C2/C3. Discogenic pain may be an underlying cause.

Spinal Nerve Compression or Tumor, Intramedullary or Extramedullary Spinal Tumor

- The dura mater of the upper cervical spinal cord is supplied by the sinuvertebral nerves C1–3[5].

Occipital Neuralgia

- Greater occipital nerve entrapment.
- The greater occipital nerve can be entrapped in its course between the obliquis capitis inferior and the semispinalis capitis. This is a commonly accepted cause of cervicogenic headaches resulting from occipital neuralgia.[7]

C2 Nerve Lesions

- Nerve-vessel compression on the C2 nerve root.
- This nerve runs across the capsule of the lateral atlantoaxial joint, and its roots are covered in the dura mater and a plexus of the epiradicular veins. Inflammatory lesions of the joint and lesions of the dura or surrounding vessels may result in compression of this nerve.[5] C2 neuralgia is characterized by intermittent and lancinating pain, unlike cervicogenic headache, because of C2/C3 facet disease, which is a constant and dull ache in nature.

Migraines and Tension-Type Headaches

- Cervicogenic headaches can be differentiated from migraine and tension-type headaches. These include:
  - Side-locked pain.

TABLE 39.1 Cervicogenic Headache International Study Group (CHISG) criteria

Major Symptoms	Pain Characteristics	Other Important Criteria	Minor Symptoms and Signs
Unilateral pain	Non-clustering episodes	Female sex	Autonomic symptoms and signs
Symptoms and signs of neck involvement*	Varying duration	Head or neck trauma	Dizziness
	Moderate, non-throbbing, non-excruciating	Pain abolished by C2 or major occipital nerve	Phonophobia and Photophobia
	Starting in the neck and spreading to the oculo-frontotemporal region		Difficulty swallowing

*a) Provocation of attacks
i) Pain triggered by neck movement; ii) pain elicited by external pressure over the ipsilateral upper, posterior neck, or occipital region.
b) Reduced range of motion of the cervical spine
c) Ipsilateral neck, shoulder, and arm pain of a rather vague, non-radicular nature
Both major criteria must be present for diagnosis: unilateral pain with at least one sign or symptom of neck involvement. Other important criteria strongly support this diagnosis.
Adapted from Sjaastad O, Fredriksen TA, Pfaffenrath V. Cervicogenic headache: diagnostic criteria. *Headache.* 1990;30(11):725–726.

TABLE 39.2 IHS International Classification of Headache Disorders 3 Diagnostic Criteria

A. Headache fulfilling criterion C.
B. Clinical and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck.
C. Evidence of causation demonstrated by at least two of the following:
   - Headache developed in a temporal relation to the onset of cervical disorder or appearance of the lesion
   - Headache significantly improved or resolved in parallel with improvement in or resolution of cervical disorders or lesions
   - Cervical range of motion is reduced
   - Headache is made significantly worse by provocative maneuvers
   - Headache was not explained by any other International Classification of Headache Disorders, 3rd edition (ICHD-3).
D. Headache abolished following diagnostic blockade of a cervical structure or its nerve supply

Adapted from the Headache Classification Committee of the International Headache Society. The international classification of headache disorders, third Edition. *Cephalalgia.* 2018;38(1):1–211.

- Can be elicited by digital pressure on neck muscles and by head movement.
- Radiation of pain in a posterior-to-anterior radiation fashion.
- Lesser degree of nausea, vomiting, photophobia, and phonophobia.[9,11]
- Not throbbing and no side shifts, unlike migraine headaches.
- Lack of response to ergotamine and triptans, unlike migraine headaches.

Investigations

A full history and physical examination are necessary for the diagnosis of cervicogenic headache. History should include:

- History of trauma (e.g. whiplash injury) or cervical disease.
- The presence of associated neurologic symptoms or stroke-like symptoms (may indicate more serious diagnoses).

Physical examination should include the range of motion of the neck and attempt to produce a typical headache with head movement or head positioning. There should be a reasonable suspicion of cervicogenic headache prior to imaging studies. Imaging modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging, may be helpful. Ultrasound may detect entrapment of the occipital nerve in occipital neuralgia. However, user variability affects reliability. CT imaging can be used to identify the bony pathology of the cervical spine. MRI is the modality of choice because it can visualize the bony pathology, soft tissue, and nerves of the cervical spine. Overall, it is important to remember that the imaging findings were not diagnostic. There should be a temporal relationship between positive findings and headaches to prove causation.

Treatment

Non-pharmacologic Treatment

Although there have been no controlled studies proving the efficacy of non-pharmacologic methods in the treatment of cervicogenic headaches, the potential benefits should still be considered.[11]

- Massage
- Cold compress
- Physical therapy, including manual therapy
  - Exercises to improve posture
  - Cranio-cervical exercises
- Transcutaneous electrical nerve stimulation therapy
- Biofeedback/relaxation therapy
- Psychotherapy

Pharmacologic Treatment

- Tricyclic anti-depressants (TCAs)
- Antiepileptic drugs[12]
  - Gabapentin
  - Carbamazepine
  - Divalproex sodium
  - Topiramate
- Serotonin and norepinephrine re-uptake inhibitors (SNRIs)
  - Venlafaxine
  - Duloxetine
- Muscle relaxants
- Nonsteroidal anti-inflammatory drugs (can be topical or enteral)[12]
  - Non-selective cyclo-oxygenase inhibitors
  - Cyclo-oxygenase-2 selective inhibitors
- Topical local anesthetics

Interventional Minimally Invasive Procedures

Cervical Facet MBB and Radiofrequency Ablation (RFA)[12]

Pain mediated by cervical facet joints can be diagnosed using a cervical MBB. Local anesthetics, with or without steroids, can be used. Patients who experience relief from this block tend to respond favorably to RFA.

Once it has been proven that the headaches are relieved by diagnostic anesthetic blockade of a specific medial branch nerve, radiofrequency ablation can be performed to provide longer-lasting relief. This is primarily used to treat cervicogenic headaches arising from the C2–C3 zygapophysial joint, whose nerve supply is via the third occipital nerve.[5] RFA of C3 and C4 medial branches can also be performed in the same setting to help with concomitant neck pain.

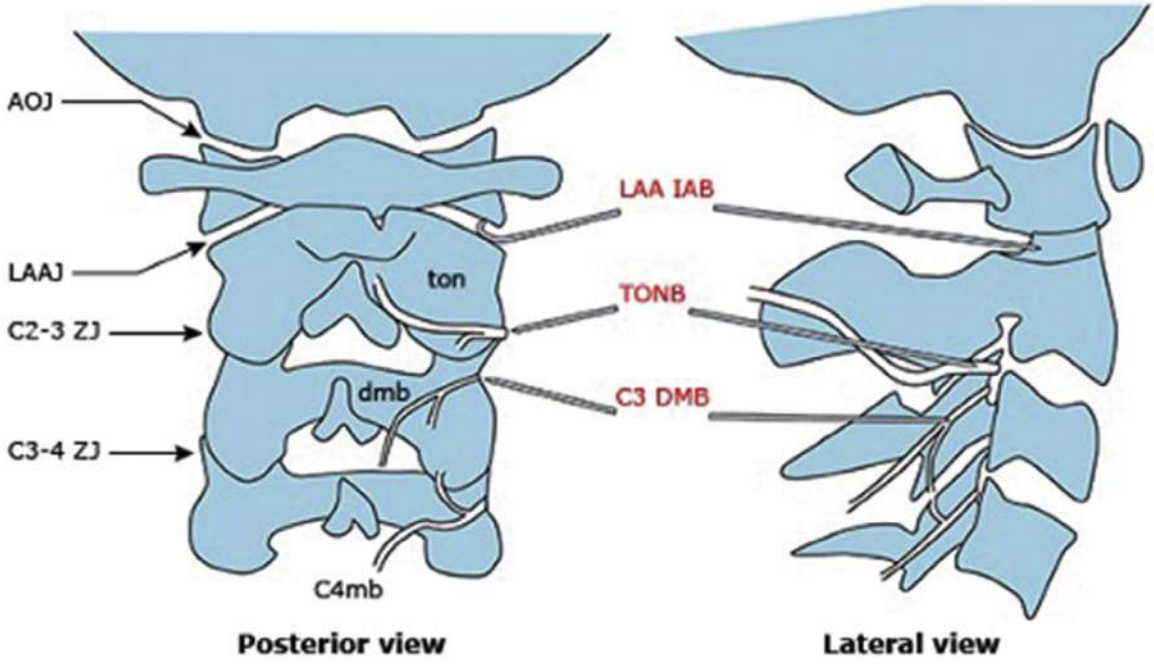
Technical Note for Cervical Facet MBB and RFA

In the posterior approach, the patient was placed in the prone position, and the facet column was identified using anterior and posterior pillar views. The needle was aimed at the "waist" of the articular pillars. A lateral view can confirm optimal positioning. The target is the middle of the articular pillars of the target vertebra.[13] The target for the third occipital nerve is the inferior aspect of C2–C3.[14] This is because the nerve usually travels along the C2–C3 joint just opposite to the center of the superior articular process of C3.[10] This is illustrated in Fig. 39.2, and the fluoroscopic images in Figs 39.3 and 39.4 highlight the needle placement targets.

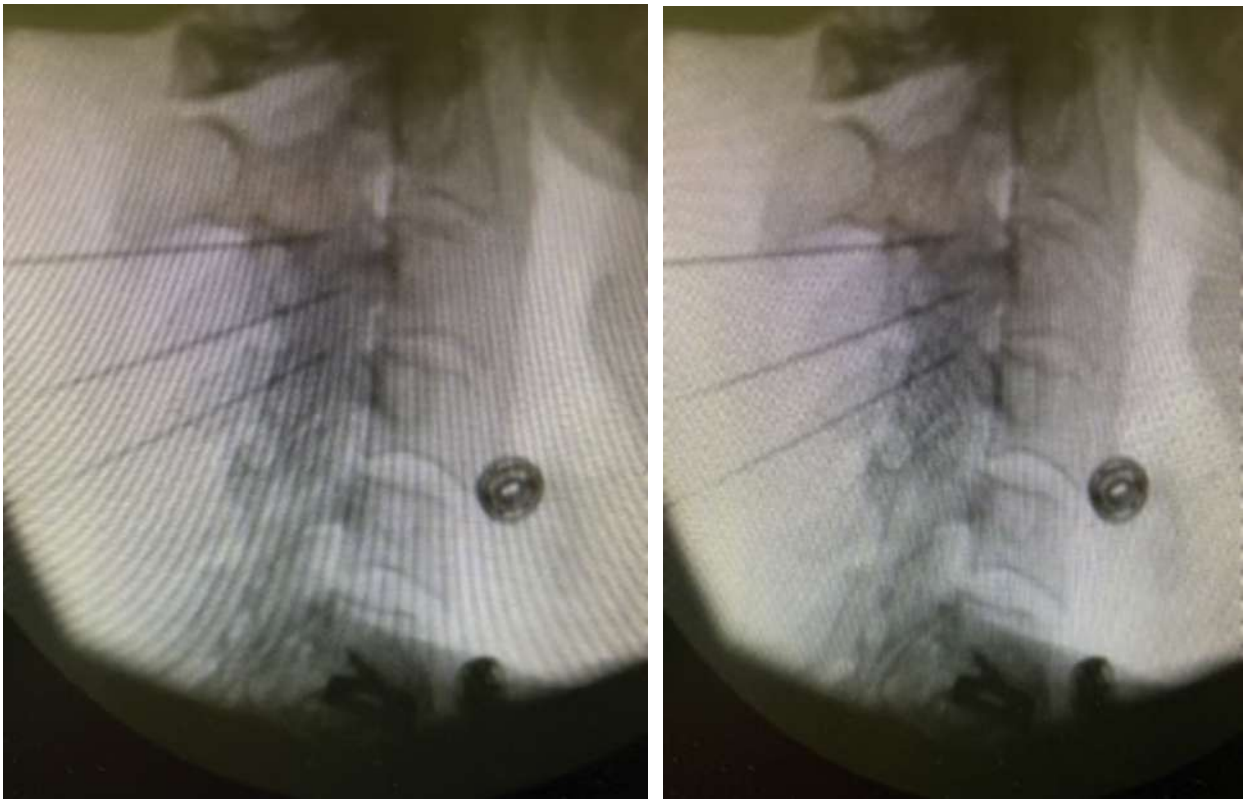
This procedure can also be performed when the patient is in a lateral position. Special precautions should be taken to ensure that the articular pillars are well superimposed, and fluoroscopy shows a true lateral image. This helps avoid faulty needle placement, which can result in spinal cord injury.

Other Interventions

- Trigger point injections (TPIs)



• **Figure 39.2** "Posterior and lateral views of the upper cervical spine, showing the leading articular sources of cervicogenic headache, the related nerves, and where needles are placed for diagnostic blocks of these structures. The red labels and needles point to target sites for diagnostic blocks." *AOJ,* Atlantooccipital joint; *C3 DMB,* C3 deep medial branch block; *C4mb,* medial branch of the C4 dorsal ramus; *dmb,* deep medial branch of the C3 dorsal ramus; *LAA IAB,* intra-articular block of the lateral atlantoaxial joint; *LAAJ,* lateral atlantoaxial joint; *ton,* third occipital nerve; *TONB,* third occipital nerve block; *ZJ,* zygapophysial joint. (Reprinted with permission from Elsevier. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. *Lancet Neurol* 2009;8:959–968.)



• **Figure 39.3** Fluoroscopic image showing the lateral view used for needle placement for the third occipital nerve and medial branch of C3 and C4 RFA. Note that the needle target for the third occipital nerve is at the middle of the C2–C3 joint. For C3–C4, the needle target is at the middle of the articular pillars.

• **Figure 39.4** Fluoroscopic image showing the anterior-posterior view used for needle placement during the third occipital nerve and medial branch of C3, C4, and C5 RFA.

It is not uncommon to have underlying myofascial pain and muscle spasms over the trapezius and cervical paraspinal muscles. Trigger point injections cause relaxation of muscle spasms, which may lead to pain relief,[11] and can help with the pain associated with myofascial pain triggers.

- Occipital nerve block[11]

The block of the greater occipital nerve in the occipital nerve entrapment can be effective in treating occipital neuralgia. The block can be performed using anatomic landmarks or ultrasound guidance. Local anesthetics can be injected with or without steroids. It can provide transient benefits in most patients, although some patients experience relief for an extended period of up to several months. If the block provides short-term relief, radiofrequency ablation using a pulsed technique or other techniques such as cryoablation can be considered for prolonged pain relief.

- Botulinum toxin[12]

Botulinum toxins can be injected into the pericranial and cervical muscles, which can potentially cause pain relief, although the Food and Drug Administration does not approve them. Further clinical studies are required to confirm its efficacy.

Surgical Treatment

Surgical intervention requires weighing the risk of worsening pain post-intervention, with the possible benefits of the procedure. There must be strong evidence of a treatable pathology on imaging and a history of pain refractory to all other treatment modalities.[12] Surgical procedures, such as neurectomy, dorsal rhizotomy, microvascular decompressing, nerve exploration and release, and joint fusion, can be considered a last resort, depending on the pathology suspected.

Efficacy of Non-pharmacologic Treatment

Generally, studies regarding the efficacy of non-pharmacologic treatment modalities have shown the greatest effect when the modes of treatment are combined. Further evidence suggests that control of cervicogenic headaches is considerable in those undergoing exercise and physical therapy programs.[13,14] Furthermore, in a randomized control trial conducted by Jull et al., long term reduction in cervicogenic headache frequency and intensity was shown to be statistically significant in those who underwent manipulative therapy and specific exercise.[15]

Efficacy of Pharmacologic Treatment and Interventional Procedures

At present, evidence of the efficacy of any pharmacologic treatment for cervicogenic headache is lacking. Therapeutic blocks of the occipital nerves have proven short term relief of symptoms, and repeated injections can lead to long term relief. Facet blocks were found to provide some acute pain relief but were less likely to have sustained benefits.[11] Overall, there is a paucity of randomized control studies that support the efficacy of interventional procedures for the treatment of cervicogenic headache.

Summary

Cervicogenic headache encompasses pain resulting from cervical spine disorders. This type of headache is more common in women and accounts for 25% of the headaches seen in chronic pain clinics. The pathogenesis of cervicogenic headaches can be explained by the overlap between the first three cervical nerves, the trigeminal nucleus, and the cervical plexus. Diagnosis can be made clinically using CHISG or HIS criteria or with relief of symptoms after a diagnostic block. History and physical examination are important for diagnosis, and more life-threatening causes should be ruled out. CT and MRI can be employed. However, this was not diagnostic. Imaging can be used to determine the presence of cervical disease. A temporal relationship is required to prove causation. Treatment can be non-pharmacologic, including massage, physical therapy, transcutaneous electrical nerve stimulation therapy, and psychotherapy. Interventional treatments such as radiofrequency ablation can be curative in patients who have complete pain relief after a diagnostic block. Surgical intervention, such as neurectomy and dorsal rhizotomy, requires weighing the risk of worsening pain post-intervention with the possible benefits of the procedure.

POST-MENINGEAL PUNCTURE HEADACHE

Louise Hillen, Deepti Agarwal

Post-Meningeal Puncture Headache

The first post-meningeal puncture headache (PMPH), also known as postdural puncture headache, was first described by August Bier in 1898 when he experienced a positional headache after undergoing a spinal anesthetic performed by his research assistant. He hypothesized that his headache was because of a loss of cerebrospinal fluid (CSF) during the spinal procedure.[16] PMPH is most commonly seen in obstetric patients following neuraxial procedures but can also be seen following interventional pain and

diagnostic lumbar puncture procedures. PMPH is a term used to describe an orthostatic bilateral headache following a meningeal puncture, and many argue that it should be termed as "meningeal puncture headache." The headache is always bilateral and is typically frontal or occipital in location.[17] Patients often present with neck stiffness, nausea, and vomiting. Other associated symptoms include vision changes (photophobia and diplopia) and auditory changes (tinnitus and hypoacusia).

Headache most commonly presents 24–48 h following a dural puncture and within 72 h in 90% of cases. However, it can occur 5–12 days after the dural puncture.[18,19] The headache generally resolves within seven days but, in rare cases, can persist for months after the initial complaint.[20] If the postural component of the headache is absent, other etiologies should be considered.[17] A PMPH can be severe and incapacitating and can greatly interfere with a parturient patient's ability to care for and bond with her newborn.[21] Among patients diagnosed with a PMPH, 39% experience at least one week of difficulty performing daily living activities.[22] PMPH can cause an increased incidence of chronic headaches, cranial nerve palsies, permanent disability, and reversible cerebral vasoconstriction syndrome.[17] Given the increase in healthcare costs and patient discomfort, prompt identification and treatment of PMPH is necessary.

Pathophysiology

Although the exact mechanism of PMPH is not fully understood, the onset of a headache is thought to be bimodal, resulting from leakage of CSF from the intrathecal space causing mechanical traction and from a reflexive cerebral vasodilation in accordance with the Monro-Kellie doctrine.[17] Both of which are caused by a disruption in the meninges that allows for leakage of CSF at a rate greater than CSF production. The average CSF volume in adults was 150 mL. It is constantly restored by the choroid plexus at a rate of 0.35 mL/min, creating 500 mL of CSF a day.[20] The absolute amount of CSF leakage is not necessarily correlated with the onset of a headache.[23] While some patients may develop a headache with small amounts of CSF leak, others may not develop a headache even with larger volumes of CSF loss. A loss of just 10% of CSF is thought to be sufficient to cause PMPH.[24]

The Monro-Kellie doctrine is a theory that the sum of the volumes of the brain, which includes CSF and intracranial blood, must remain constant. To maintain a constant intracranial volume, compensatory vasodilation of intracranial vessels occurs when CSF volume loss occurs. The increase in blood volume due to cerebral vasodilation activates the trigeminovascular system, leading to pain similar to that of migraine. The trigeminothalamic tract delivers signals to the thalamus and refers to pain to the ophthalmic branch and the first three cervical roots. Evidence of the Monro-Kellie doctrine is thickened meninges secondary to dural venous dilation observed on MRI in patients with PMPH.[25]

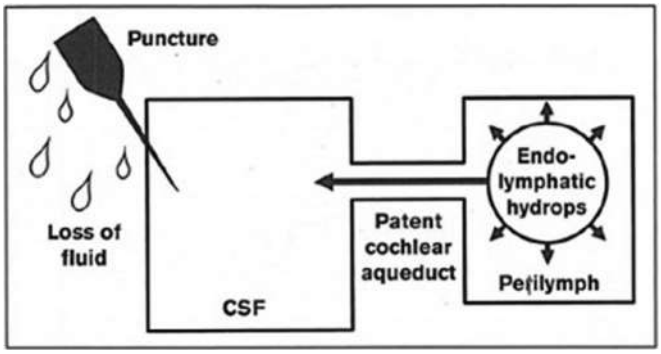
Secondary causes of PMPH are likely due to the relative CSF hypotension. CSF loss leads to a lower hydrostatic pressure, causing a loss of buoyant support and allowing the brain to sag while in the upright position.[26] The higher the level of the meningeal puncture, the less hydrostatic pressure at the puncture site. This explains why cervical meningeal punctures are much less associated with PMPH than lumbar punctures. Uncompensated CSF loss leads to a decrease in the subarachnoid pressure. The normal CSF opening pressure in the horizontal position is 70–180 mmH_20.[12] An opening pressure of 60 mmH_20, defined as CSF hypotension, is often present in PMPH but is not consistently correlated with the presence of symptoms.[27]

Although the absolute volume of CSF loss does not correlate with a PMPH, a sudden loss of CSF volume and a change in pressure between the inside and outside of the intracranial venous structures are thought to result in venous dilation.[28] Furthermore, a sudden loss of CSF results in a downward pull on pain-sensitive structures (dura, bridging veins, cranial nerves, venous sinus) when the patient is in an upright position.[28] This is exacerbated by a redistribution of CSF downward toward the spinal dural sac, worsening the stretch and tension on the meninges, intracranial vessels, and nerves. This theory is supported by radiographic evidence of downward displacement of intracranial structures following a PMPH.[25] Traction on the bridging veins can lead to a tear in the dura, potentially causing a subdural hemorrhage.[29] A cohort study of over 26 million deliveries suggests a small but statistically significant increased risk of diagnosis of intracranial subdural hematoma in obstetric patients with PMPH.[30]

CSF hypotension and the resulting traction often result in cranial nerve palsies (Table 39.3). The abducens nerve (CN VI) is most frequently affected because of its acute angulation near the point of fixation of the cranium and the petrous bone, resulting in increased traction.[31,32] Diplopia often occurs due to abducens nerve traction and subsequent paralysis of the lateral rectus muscle of the eye. Permanent vision damage is rare, and diplopia typically resolves within two weeks to eight months.[33] The facial nerve (CN VII) is also frequently affected and can result in paralysis of facial muscles, disruption of lacrimal and salivary gland function, and loss of taste in the anterior two-thirds of the tongue.[31] Changes in hearing can occur because of the effects on the vestibulocochlear nerve (CN VIII). A cochlear aqueduct connects the perilymphatic space to the CSF-filled subarachnoid space. CSF pressure changes are transmitted to the perilymphatic space (Fig. 39.5).[34] A loss of CSF pressure through a patent cochlear aqueduct can lead to perilymphatic hypotonia and endolymphatic hydrops, resulting in low-frequency hearing loss and tinnitus.[35] The ophthalmic branch

TABLE 39.3 Commonly Affected Cranial Nerves in Post-meningeal Puncture Headaches

Cranial Nerve	Symptomatology
Trigeminal Nerve (CN V) • Ophthalmic Branch (V1) • Maxillary Branch (V2) • Mandibular Branch (V3)	• Frontal pain • Sensory changes to all three branches, without motor involvement • Tongue numbness
Abducens Nerve (CN VI)	• Ocular abnormalities • Double vision • Deviated gaze because of lateral rectus muscle weakness • Photophobia
Facial Nerve (CN VII)	• Paralysis of the facial nerve • Loss of taste to anterior 2/3 of tongue • Interruption of lacrimal and salivary gland function
Vestibulocochlear (CN VIII)	• Changes in hearing • Low frequency hearing loss • Tinnitus
Vagus Nerve (CN X)	• Nausea and vomiting because of chemoreceptor triggering in the medulla • Occipital and posterior fossa pain



• **Figure 39.5** Mechanism of hearing loss and tinnitus after meningeal puncture. (From Michel, Olaf, and Tilman Brusis. Hearing loss as a sequel of lumbar puncture. *Ann Otol Rhinol Laryngol.* 1992;101(5):390–394.)

(V1) of the trigeminal nerve (CN V) innervates the bridging veins and dura and refers to pain in the frontal region. Vagus nerve (CN X) traction can also be responsible for nausea and vomiting due to stimulation of the chemoreceptor regions in the medulla. The vagus nerve also refers to pain in the posterior fossa and occipital regions. Traction of the upper cervical nerves can also manifest as shoulder stiffness and occipital and cervical pain. Rare case reports have suggested optic nerve (CN II) and trochlear nerve (CN IV) involvement (please refer to Table 39.3 for a summary).[31]

The Role of Arachnoid Matter in the Pathogenesis of CSF Leak

The dura mater is roughly 400 μm thick and comprises fibers distributed in a random organization of roughly 80 concentric layers called dural laminas.[36] The dural layer is elastic in nature compared with the more structured arachnoid membrane, and has the primary purpose of acting as a barrier to limit the escape of CSF fluid. Electron microscopy has demonstrated that tight junctions are present in the outer layer of the arachnoid, similar to that of the capillary endothelium of the brain, whereas the dura does not contain tight junctions.[37] This supports the concept that a puncture in the arachnoid mater, a typically impermeable layer that prevents the spread of CSF, rather than a puncture in the dura, is the primary cause of PMPH.

Dura Mater and Response to Trauma

Following neurosurgery, dura mater closure and healing are vital to prevent CSF leakage and infection. If the dural gaps are small, conservative management can be the treatment of choice. However, larger dural gaps necessitate direct repair or via the application of synthetic or biologic graft materials. It was first thought that fibroblastic proliferation from the edge of the dural tear facilitated dural closure.[38] In 1959 Keener showed that fibroblastic proliferation surrounding blood clots and tissue of the pia and arachnoid mater helped promote dural closure.[38] Therefore only minimal trauma to the dural layers and adjacent tissue would likely not promote substantial dural healing.

Diagnosis

The third edition of the International Classification of Headache Disorders defines a diagnosis of PMPH as a headache that occurs within five days of a dural puncture and resolves spontaneously within 14 days or with the closure of the epidural leak with an autologous epidural lumbar patch.[39] The period in which the headache develops is debatable and can occur within one–12 days of insult to the meninges. Headaches must fulfill the criteria that symptoms are attributed to low CSF pressure, which is an orthostatic headache accompanied by neck pain, changes in hearing, sunlight sensitivity, nausea, or vomiting.[39] The orthostatic nature of the headache means that symptoms significantly worsen with standing or sitting and improve after moving in a supine position. Prior editions of the International Classification of Headache Disorder criteria included a postural headache occurring within 15 min in the upright position and resolving within 15 min in the supine position. The headache improved once the CSF pressure returned to normal. Brain imaging may show brain sagging or pachymeningeal enhancement. Spine MRI may be notable for extradural CSF.[39]

It is important to rule out other causes of headaches. Further evaluation is needed if the headache is constant, unilateral, or presents with new-onset nausea or vomiting. Neurologic consultation and further diagnostic imaging are warranted in patients with altered mental status, seizures, or sensory/motor deficits. The differential diagnosis of a headache that develops or does not meet the classic diagnostic criteria of PMPH includes intracerebral hemorrhage, cerebral venous thrombosis, infection, eclampsia, caffeine withdrawal, and subdural hematoma.[40,41]

Incidence and Risk Factors

The incidence of PMPH ranges vastly from 1%–63%, and varies based on the patient characteristics, technique used, and needle size and design.[42] A trial by Vandam and Dripps in 1956 followed 10,098 spinal anesthetics and found an 11% incidence of PMPH, of which 0.4% were associated with ocular difficulties and 0.4% with auditory difficulties.[43] The greatest incidence of PMPH occurred in patients in the third and fourth decade of life and was twice as common in women (14%) than men (7%).[43] In a study of 27,064 obstetric patients undergoing a neuraxial procedure, 142 developed a post-dural puncture headache.[44] Eight of these were described as atypical, meaning the postural component of the headache did not exist despite other associated symptoms and improvement with an epidural blood patch (EBP).[44] Choi et al. found that the highest risk group of patients is the obstetric population, in which 1.7% of parturients will experience PMPH following spinal anesthesia with a 27-gauge Whitacre needle.[45] The incidence of accidental dural puncture with epidural placement is around 1.5%, with over half of these patients developing PMPH.[45]

Medicolegal analysis of outpatient procedures from 2009–2017 showed that interlaminar epidural injections at both the cervical and lumbar levels were most commonly associated with claims of unintentional dural puncture.[46] Among 10,000 fluoroscopic-guided interlaminar epidural injections, the incidence of inadvertent dural puncture was 0.5% overall, 1% in the cervical region, 1.3% in the thoracic region, and 0.8% in the lumbar region.[47] The incidence of PMPH in these patients was not followed.[47] The incidence of PMPH following intrathecal drug delivery systems is approximately 23%.[48] While most of these patients' symptoms were self-limited and resolved with conservative management, 21% of patients required an EBP or fibrin glue patch procedure.[48]

Patient risk factors for the development of PMPH include female sex, age (third to fourth decade of life), pregnancy, history of headaches, preexisting CSF hypotension, and low body mass index. Although the physiology resulting in the disparity among

genders is not fully understood, a large meta-analysis concluded that compared to males, nonpregnant females have double the risk of developing a PMPH.[49] Young age is also thought to be an independent risk factor for the development of a PMPH, possibly because the dura is more elastic and has a higher likelihood of maintaining a patent dural opening than the less elastic dura in older patients.[50] A medical history of PMPH and headaches prior to the procedure is also associated with an increased risk of PMPH after dural puncture.[51] Obesity is protective against the development of a PMPH because the increased epidural pressure decreases the gradient across the dural puncture, allowing less CSF to leak.[52] An increased abdominal pressure may also help seal a defect in the dura and decrease CSF loss.[52]

Modifiable risk factors for PMPH include the number of attempts and needle design, size, shape, and bevel direction. Spinal needles can be designed with cutting bevels, such as the Quincke-type, or as a pencil point, such as the Whitacre-type and Sprotte.[53] A systematic review of 25 randomized controlled trials comparing cutting and pencil point needles concluded that pencil point (non-cutting) needles had a much lower rate and incidence of PMPH and subsequent need for EBP.[54] The risk of PMPH following a puncture with a 20 to 22- gauge cutting needle is ~36%, compared to ~2% with a 22-gauge non-cutting needle.[55] The risk of PMPH is directly correlated to the diameter of the needle used, with smaller gauge needles having a lower incidence. Most unintentional dural punctures occur during epidural placement with a 17- or 18-gauge Tuohy cutting needle. Angle et al. found reduced CSF leakage with a 20-gauge Tuohy compared to a 17-gauge.[56] similarly, a cadaver study showed a six-fold greater mean CSF leak when using a 22-gauge needle compared to a 25-gauge needle.[57] Cutting needles have an increased rate of PMPH, likely because of its potential to cut dural fibers, whereas a pencil point blunt tip divides but does not disturb the continuity of the dural fibers.[57] Electron microscopy revealed that a blunt tip could cause an irregular hole in the dura, whereas a clean hole is produced by a cutting needle.[55] The irregular hole in the dura may promote an inflammatory reaction that promotes healing and hole closure.

Electron microscopy studies have shown that dural fibers are collagen and lack a specific orientation, whereas the arachnoid mater cells are oriented parallel to the long axis of the spinal cord. The orientation in which the bevel is directed compared to the dural fibers has been proposed to affect the amount of CSF leakage and subsequent headache risk. *In vitro* studies by Cruickshank and Thompson showed that fluid loss was not reduced when the bevel of the needle was aligned parallel to the longitudinal direction of the fibers. However, 22-gauge Whitacre point needles produced less fluid loss than a 22-gauge Quincke point needle inserted across the fibers, suggesting that the leakage rate was related to needle design, not to the alignment of a bevel point.[58] In contrast, a five study meta-analysis demonstrated that insertion of a beveled or cutting needle oriented parallel to the long axis of the spinal cord is associated with a statistically significant decrease in the incidence of PMPH than that inserted perpendicularly.[59] Norris et al. compared epidural catheter placement in two groups: one in which the bevel of the Tuohy was parallel to the dural fibers and one in which the Touhy was perpendicular to the long axis of the spinal cord. There was a similar rate of unintentional dural puncture. However, the intensity of PMPH was much lower in the parallel orientation group, requiring fewer EBPs.[60]

Proceduralist characteristics may also play a role in the development of PMPHs. There is a higher incidence of PMPH after a diagnostic dural puncture performed by a neurologist or neuroradiologist, likely because of the higher gauge needles required and possibly because of less experience in performing the procedure.[61] In a prospective study of 80 adult patients, the incidence of PMPH following a diagnostic lumbar puncture was 33%.[62] Diagnostic lumbar punctures often require a 20- or 22-gauge needle to measure opening pressure and obtain CSF over a brief period. If needles are less than 22 gauge, the collection of just 2 mL of CSF can take at least 6 min, and measuring the opening pressure can be very challenging.

Prevention

As mentioned before, PMPH prevention depends on needle characteristics and, probably, bevel orientation during dural puncture. Using the smallest pencil point needle parallel to the longitudinal access of the spinal cord will help decrease the incidence of PMPH. It is controversial whether the placement of an intrathecal catheter after an unintentional dural puncture during epidural placement can reduce the risk of PMPH. Many of the available studies are retrospective in design and cannot be randomized. Ayad et al. found a reduction in the incidence of PMPH from 81%–31% if an intrathecal catheter was placed but removed immediately after delivery, and an incidence of 3% if the catheter was left in for 24 h post accidental dural puncture.[63] In 173 patients who had an accidental dural puncture, 73 had an intrathecal catheter placed that remained in situ for 36–48 h, resulting in a 36% incidence of PMPH. This is compared to a 59% incidence in 99 patients who had an epidural catheter placed at a different level or just a single shot spinal administered through the Tuohy needle itself.[64] Furthermore, the severity of PMPH and requirement of analgesics was significantly less in the intrathecal catheter group.[64] A 2017 meta-analysis of over 1,000 patients in 13 studies showed a decreased risk for PMPH and need for an EBP in patients receiving an intrathecal catheter than a replacement epidural catheter group.[65]

A survey of North American obstetric anesthesiologists suggested that 75% would replace the catheter epidurally after an accidental dural puncture and 25% would place it intrathecally, even though 76% believed that leaving the intrathecal catheter in place for 24 h would reduce the incidence of PMPH.[66] The most important reason that an intrathecal catheter may not be placed following an inadvertent dural puncture is the safety of the intrathecal catheter. There is a high potential risk of misuse because of the lack of familiarity with intrathecal catheter dosage and usage. Although it may be beneficial to leave an intrathecal catheter in place for 24 h to reduce the incidence and severity of PMPH, it is often removed at most institutions because of safety concerns.

The use of a prophylactic epidural blood patch (PEBP) following an accidental dural puncture (ADP) is controversial because of the lack of strong literature. Some retrospective studies have shown that PEBP can decrease the severity, duration, or need for a therapeutic blood patch. A randomized, controlled, double-blinded study by Scavone et al. assessed the efficacy of PEBP in 64 parturients who had an unintentional dural puncture with a 17-gauge Tuohy.[67] After delivery, all patients had 20 mL of autologous blood drawn, which was either administered or not via a sham procedure. There was no difference between the two groups in the rate of headache, peak pain scores, or the need for a therapeutic blood patch, although the median duration of the headache was shorter in the PEBP group.[67] Other studies have shown that prophylactic epidural or intrathecal saline (typically 10cc) failed

to show a decreased need for a therapeutic blood patch.[68] An additional analysis of five studies involving 221 patients from the obstetric and surgical population showed insufficient evidence to recommend a PEBP.[69] Overall, PEBP does not appear to decrease the incidence of PMPH or eventual need for a therapeutic blood patch after an unintentional dural puncture.

Neuraxial morphine administration for prophylaxis following an unintentional dural puncture is controversial. In a randomized controlled trial by Al-Metwalli, a 3 mg dose of epidural morphine was administered immediately following an unintentional dural puncture and again at 24 h, demonstrating a decrease in PMPH from 48% to 12%.[70] However, a randomized, double-blind study by Peralta et al. showed that 150 μg of intrathecal morphine administered after delivery in patients with an ADP did not decrease the incidence or severity of PMPH discounting the prophylactic use of intrathecal morphine.[21] Furthermore, Brinser et al. demonstrated that both epidural and intrathecal administration of morphine following inadvertent dural puncture did not decrease the risk of PMPH.[71] It is important to recognize that neuraxial morphine is not without risks, including respiratory depression, nausea, vomiting, and itching. Caution must be taken when administering epidural morphine, especially after a dural puncture, since there may be translocation into the intrathecal space at unknown concentrations.

Recent attention has been given to the administration of cosyntropin, an adrenocorticotropic analog, following ADP for prophylaxis against PMPH. The mechanism by which adrenocorticotropic hormone (ACTH) could improve PMPH is not fully understood but is thought to be due to ACTH stimulation of aldosterone, which enhances salt and water retention, expands blood volume, and favors the closure of a dural tear. ACTH may also increase CSF production because of the active transport of sodium ions into CSF and possibly an increase in β-endorphins that modulate pain perception.[72] In a study of 95 patients who received 1 mg of cosyntropin following an ADP, the incidence of PMPH was halved from 69% with placebo to 33% with cosyntropin, and the need for an EBP was reduced from 30% to 11%.[73] Aside from rare hypersensitivity reactions, the risk associated with administering cosyntropin is low.

Treatment

Once the diagnosis of PMPH is established, treatment should be initiated. It is reasonable to start with conservative treatment options since 85% of PMPHs last less than five days and are rarely associated with significant morbidity.[74] Though recumbent bed rest may improve the symptoms of PMPH, a meta-analysis by Thoennissen et al. failed to show that recumbent bed rest reduced the incidence of PMPH more than immediate mobilization.[75] A survey of 1,024 anesthesiologists noted that aggressive hydration and bed rest were most commonly used as prophylactic measures to prevent PMPH following an inadvertent dural puncture. The same study concluded that the most frequently used treatment options were aggressive hydration, oral caffeine, oral non-opioid analgesics, and EBP procedures.[76] Though aggressive hydration is commonly recommended, there is no evidence to support it. While many physicians would encourage a patient to use conservative management for 24–48 h prior to recommending an EBP, some would argue that this can be particularly disabling if that patient is postoperative or in the postpartum period. Many pharmacologic agents have been studied for the treatment of PMPH. These include methylxanthines (caffeine and theophylline), serotonin agonists, anti-convulsant agents, adrenocorticotropic hormone, and corticosteroids.

Caffeine is a potent methylxanthine central nervous system stimulant that causes cerebral vasoconstriction. It is the most widely used pharmacologic treatment for PMPH. Caffeine can be administered at an oral dose of 300 mg or an intravenous dose of 500 mg caffeine sodium, equating to 250 mg caffeine.[77] While caffeine is considered safe in most patients, there have been reports of seizures associated with its use, and caution must be used in patients with a history of seizures. Careful use is also necessary for patients with hypertension, disorders of pregnancy-induced hypertension, anxiety, and arrhythmias. Sechzer showed that 75% of women receiving intravenous caffeine did have some temporary relief from their PMPH, supporting its use.[78] Jarvis et al. revealed that over 70% of women had improvement in their pain scores four h after intravenous caffeine infusion.[79] Additionally, 300 mg oral caffeine showed a decrease in pain scores at 4 h, but not at 24 h.[77] These studies ultimately show that the effects of caffeine are transient, and administration may need to be repeated. Caffeine administration does not appear to decrease the need for an eventual blood patch. Theophylline, another cerebral vasoconstrictor, has not been widely studied or supported by the literature.

Serotonin receptor agonists, such as sumatriptan, cause cerebral vasoconstriction and are often used to abort migraines. While there has been no evidence to support its use in the treatment of PMPH, a non-randomized study suggested that frovatriptan was useful in the prevention of PMPH in patients undergoing diagnostic lumbar punctures.[80] More studies are needed to evaluate serotonin receptor agonists in other patient populations.

Anti-convulsant agents such as gabapentin and pregabalin may be helpful in the treatment of PMPH. Pregabalin is a ligand of voltage-dependent calcium channels that reduces calcium influx at nerve terminals and attenuates the release of glutamate, substance P, and norepinephrine at the synapses. In a study of 40 patients experiencing a PMPH after spinal anesthesia or a lumbar puncture, half were assigned to receive 150 mg/day of oral pregabalin for three days, then 300 mg/day for two additional days, while the other half received placebo for the same length of time.[80] The pregabalin group had significantly lower pain scores after the second day of treatment and required less diclofenac for additional pain control.[81] An additional study of 42 patients showed that compared to the use of ergotamine and caffeine, patients taking gabapentin had significantly less pain, nausea, and vomiting following an ADP.[82] While these studies looking at pregabalin and gabapentin are promising, more studies are needed to demonstrate its efficacy.

Cortiosteroidogenic analogs (ACTH, cosyntropin, and tetracosactrin) have been studied for the treatment of PMPH. A prospective, randomized, double-blind study showed that a 1 mg single depot injection of the ACTH analog tetracosactrin did not decrease the severity of headache or the need for an EBP.[83] Further studies have shown that patients receiving an EBP following the development of PMPH had significant improvement in pain and function scores in patients receiving cosyntropin on day one of symptoms. However, cosyntropin showed similar efficacy to the blood patch group immediately after treatment and at days three and seven.[84] While these limited studies show some improvement with cosyntropin use, there is a question of its overall efficacy.

Once a patient has failed medical and conservative management, it is reasonable to consider more invasive options. Epidural treatments for PMPH include the use of saline, colloids, fibrin glue, and blood. The gold standard treatment is EBP, which entails

injecting a small amount of autologous blood into the epidural space. EBP offers a promising and immediate resolution of symptoms in approximately 61%–98% of patients.[85] Contraindications to a blood patch are similar to those of any neuraxial procedure. The first contraindication was patient refusal. If a patient has religious concerns about blood transfusion, alternative patching materials can be offered. The coagulation status of the patient must be reviewed to minimize the risk of epidural hematoma. An EBP should not be performed on patients who are septic, āre bacteremic, or have a localized infection at the injection site to prevent the introduction of bacteria into the epidural space. It is safe to perform an EBP in patients who are HIV positive because HIV naturally crosses the blood–brain barrier; thus there is no increased risk of introduction centrally during the procedure.[86]

The technique of EBP was first described by Gormley in 1960 and is based on the placement of a single shot epidural.[85] The procedure typically requires two people: one to locate the epidural space and the other to draw the blood. Sterility is of utmost importance during both epidural placement and blood collection. The patient can either be supine or in the lateral decubitus position, depending on the patient's tolerance. It is wise to select a site that is caudal to the suspected dural tear since 15 cc of epidural blood will spread roughly six segments cephalad and three segments caudad.[87] Additionally, more caudal levels are associated with less cord compression. After EBP, the patient remained supine with his legs slightly elevated. Martin et al. found that 2 h in the supine position after EBP provided the patient with 100% relief versus 60% in a group that remained supine for only 30 min.[88]

The mechanism of action of EBP is not fully understood, but appears to be due to two separate mechanisms. The first and initial effects can occur within minutes and are likely due to compression of the dura toward the spinal cord and the reduction of intradural volume. MRI analysis of five patients following EBP placement showed large extradural collectures with an anterior displacement of the thecal sac and a mean spread of 4.6 vertebral spaces.[89] This epidural spread following an EBP is longitudinal and circumferential, helping to envelop the entire dural sac. The reduction in the intradural volume shifts the CSF more cephalad, re-suspending the brain, and reducing traction. In accordance with the Monro-Kellie rule, an increase in intracranial CSF helps to reduce cerebral vasodilation and intracranial blood volume.

While patients often report instant relief in their symptoms because of these effects, post-blood patch MRI studies have shown that these compressive mass effects disappear by 7 h after the procedure.[90] A second and more long-lasting effect is likely due to the sealing of the dural or arachnoid tear with a gelatinous plug, preventing further loss of CSF. The blood patch acts as a temporary plug until permanent repair of the meningeal puncture can occur. Failure of self-closure of the dural or arachnoid tear can result in EBP failure despite initial relief. Optic nerve sheet diameter (ONSD) is a surrogate marker of intracranial pressure and has been studied in patients undergoing EBP procedures. Dubost et al. found that the ONSD increased in patients who had a successful EBP but not in patients who had EBP failures.[91] This suggests that a sustained increase in intracranial pressure is associated with a successful EBP.

The ideal volume of blood to draw and inject during an EBP is ~20 mL, stopping on injection if the patient complains of back, buttocks, or neck pain. There appears to be no relation to the volume of blood injected and EBP success rate.[92] In a multinational, multicenter, randomized, blinded trial to determine the optimum volume of autologous blood for an EBP, 121 patients experiencing symptoms after an ADP were allocated to receive 15, 20, or 30 mL of blood.[93] Only 54% of patients in the 30 mL group were able to receive the entire volume because of pain on injection, while 81% in the 20 mL and 98% in the 15 mL group were able to tolerate receiving the allocated volume.[93] Interestingly, the 20 mL group had the highest incidence of permanent or partial relief, at 73%, while the 15 mL and 30 mL groups had an incidence of 61% and 67% relief, respectively.[93] This study confirms that 20 mL of autologous blood appears to be the optimal volume for placement of an EBP. Chen et al. found that 7.5 mL of autologous blood was comparable to 15 mL of blood in its analgesic effect but with less nerve root irritation during injection.[94] Further studies on optimal blood volume in the nonobstetric population are warranted.

Alternative patching materials include epidural fibrin glue and epidural dextran-40. Although these materials have been successfully employed, they are not widely used owing to their cost and safety concerns. Dextran-40 appears to be a safe alternative for Jehovah's Witnesses. Epidural saline blouses or infusions are ineffective alternatives and often result in more interventions with a lower success rate because saline is quickly absorbed from the epidural space. As a last resort, surgical repair of the dural tear may be considered and is typically reserved for severe cases of chronic PMPH that have failed management with an EBP.

The optimal timing of EBP remains controversial. Placement of EBP too early in PMPH symptomatology is thought to be associated with an increased risk of EBP failure. In a 13-year retrospective review of 129 patients, the success rate for permanent relief of PMPH from an EBP was 86% in patients receiving it 48 h after a neuraxial procedure, 65% in patients receiving it at 24–28 h, and only 50% in patients receiving it within 24 h.[95] This may be confounded because patients with worse symptoms and CSF leakage may require an EBP earlier, and subsequent patches may be necessary to help with closure of the dural puncture.

EBP is typically considered a safe treatment option. The most common side effects of EBP are low back and radicular pain because of an inflammatory response and nerve root compression, which tends to resolve spontaneously or with nonsteroidal anti-inflammatory drugs.[96] Rare but possible complications include epidural hematoma, infection, and arachnoiditis because of unintentional subdural or subarachnoid injection of the blood. Two cases of facial nerve paralysis following EBP have been reported, both of which resolved spontaneously.[97]

While EBP is considered the gold standard for the treatment of PMPH, sphenopalatine ganglion block (SPGB) has been suggested as a simple and minimally invasive alternative to an epidural blood patch. The mechanism of SPGB, which was first described in 1909, is thought to be related to cerebral vasoconstriction.[98] The sphenopalatine ganglion is a collection of parasympathetic fibers located bilaterally in each pterygopalatine fossa. With the loss of CSF, this ganglion is activated, releasing acetylcholine, nitric oxide, and vasoactive peptide, causing vasodilation of dural blood vessels.[98] Blocking these ganglions with intranasal lidocaine decreases nociceptor signaling and blocks cerebral dural vasodilation, relieving the PMPH.[99] The traditional approach to an SPGB involves introducing a cotton-tipped applicator soaked in a local anesthetic solution into the nares. The SPGB can be repeated at 20 min intervals, usually up to two times, if the resolution of headache symptoms is not achieved. In a 17-year retrospective chart review, more patients received relief from their headache symptoms at 30 min and 1 h in the SPGB group than in the EBP group with equal recovery at 24 h, 48 h, and one week.[99] Patients who received an EBP required more return visits

to the emergency department than the SPGB group.[99] A clinical trial comparing the use of saline versus lidocaine for an SPGB did not show any significant difference in pain intensity at 30 min, with similar pain reduction and avoidance in an EBP, suggesting that the major effect of the SPGB may not necessarily be because of the local anesthetic used.[100] SPGB appears to be a safe and useful alternative for patients who have contraindications or may be reluctant to undergo an EBP.

PMPH Summary

PMPH and its management are well-known and widely accepted entities in anesthesia entities. With better awareness of the risk factors related to PMPH, clinicians need to be vigilant when performing neuraxial techniques. Although nonfatal, it can cause significant morbidity and should be treated seriously. In the setting of a dural puncture or inadvertent puncture with pathognomonic symptoms, the diagnosis of PMPH is straightforward. Treatment should start with conservative therapy as the headache is generally self-limiting within 7–10 days. EBP is the gold standard and the most effective treatment modality for PMPH. Surgical repair may be required in patients with chronic PMPH. Newer treatment modalities are available, but high-level evidence supporting their efficacy is still needed.

SPONTANEOUS INTRACRANIAL HYPOTENSION

Dost Khan

SIH was initially described by Schaltenbrand in 1938 and is characterized by symptoms similar to dural puncture headache, but in the absence of dural puncture. The incidence is approximately five per 100,000 person-years. Women are affected twice as often as men, and the peak incidence is in the fourth or fifth decade of life.[101]

Clinical Symptoms of SIH

This syndrome is usually suspected in patients with postural headaches after a fall, trauma, whiplash, exercise, or violent coughing. Although classically postural, the headache can be nonpositional or even paradoxical (worse when lying down).[102] The headache can be gradual or thunderclap in onset and has also been described as exertional, intermittent, or mainly occurring at the end of the day. Headache results from the downward displacement of the brain from the loss of buoyancy with traction on pain-sensitive structures, including the dura. Another mechanism is the compensatory dilation of the pain-sensitive intracranial venous structures. Additional symptoms include neck pain, stiffness, nausea, vomiting, blurred vision, tinnitus, vertigo, and photophobia. Tinnitus is secondary to the transmission of the abnormal CSF pressure to the perilymph,[103] while vision and balance abnormalities are because of stretching of the optic and vestibulocochlear nerves. Cranial nerve (CN) palsies leading to ophthalmoplegia can involve the oculomotor (CN III), trochlear (CN IV), or abducens nerve (CN VI), with CN VI being the most commonly affected.[104] Hyperprolactinemia and galactorrhea can result from distortion of the pituitary stalk.[105] Symptoms referable to the spine include back pain and radiculopathy, presumably due to compression of the nerve roots or spinal cord by the leaked CSF. The International Classification of Headache Disorders has published diagnostic criteria for SIH (Table 39.4),[106] although some experts consider the criteria too restrictive.[107] The differential diagnoses of SIH include primary (new daily persistent headache) and secondary headache disorders. Secondary headaches to be considered are subarachnoid hemorrhage, subdural hematoma, carotid/vertebral artery dissection, cerebral venous sinus thrombosis, benign intracranial hypotension, posttraumatic headache, meningitis, and postural orthostatic tachycardia syndrome.[101]

TABLE 39.4 Diagnostic Criteria for Headache Attributed to Low Cerebrospinal Fluid (CSF) Pressure

A. Any headache fulfilling criterion C
B. Either or both of the following:
   a. Low cerebrospinal fluid (CSF) pressure (<60 mm CSF)
   b. Evidence of CSF leakage on imaging
C. Headache has developed in a temporal relation to low CSF pressure or CSF leakage or led to its discovery.
D. Not better accounted for by another ICHD-3 diagnosis.

Criterion C
Evidence of causation was demonstrated by at least two of the following: 1. Headache has developed in temporal relation to the onset of non-vascular intracranial disorder or has led to its discovery; 2. Either or both of the following: a) headache has significantly worsened in parallel with worsening of the non-vascular intracranial disorder, b) headache has significantly improved in parallel with the improvement in the non-vascular intracranial disorder; 3. Headache has characteristics typical of non-vascular intracranial disorder; 4. There is also evidence of causation.

From: Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, third edition. *Cephalalgia.* 2018;38(1):1–211.

The most common cause of SIH is leakage of the CSF through an incompetent dura, either because of an overt dural tear, presence of a meningeal diverticulum, through dural defects along nerve root sleeves, or perineural cysts (Tarlov cysts). In an observational study of 568 patients with SIH, Schievink et al. classified the cause of spinal CSF leaks into four categories: Type 1 (dural tear) occurred in 26.6% of patients; Type 2 (meningeal diverticula) occurred in 42.3%; Type 3 (CSF-venous fistula) occurred in 2.5%; and Type 4 (indeterminate type) occurred in 28.7% of patients.[108] Secondary dural injuries have been reported because of vertebral osteophytic spurs[109,110] and herniated or calcified degenerative discs piercing the dura.[111] The onset of symptoms can be precipitated by a fall, trauma, or exercise. SIH appears to be associated with generalized connective tissue disorders, ascribed to compromised elastic fiber integrity and spatial disorganization of dural tissue, as seen in mouse models.[101,112,113] These include Marfan syndrome, Ehlers-Danlos syndrome type II, Loeys-Dietz syndrome, autosomal dominant polycystic kidney disease, isolated joint hypermobility, joint hypermobility with fascial thinning, and spontaneous retinal detachment.

Diagnosis of SIH

The diagnosis of SIH is suspected with low CSF pressure on diagnostic lumbar puncture and meningeal enhancement on MRI of the cranium. Diagnostic lumbar puncture usually shows a low CSF pressure (<60 mm H_2O; reference range, 65–195 mm H_2O). However, normal to high CSF opening pressure has been reported with lumbar puncture, suggesting that low CSF volume, rather than pressure, may be the principal pathophysiologic driver.[114] CSF protein, red cell, and white cell counts are usually increased, postulated to decrease CSF flow in the setting

of increased permeability of dilated meningeal vessels. Brain MRI shows meningeal enhancement, subdural fluid collection, caudal displacement of the cerebellar tonsils, and pituitary abnormalities (enlargement or hyperemia) (Fig. 39.6).[101,109] Scheivink noted five characteristic features of SIH: (a) subdural fluid collections, (b) enhancement of the pachymeninges, (c) engorgement of venous structures, (d) pituitary hyperemia, and (e) sagging of the brain (mnemonic: SEEPS).[101] Meningeal enhancement is usually thickest in patients with low intracranial pressure and subdural fluid collections. A relationship between SIH, subdural fluid collection, and subdural hematoma has been noted.[115,116,117] Spine MRI of patients with SIH usually shows epidural or paraspinal fluid collections and collapse of the dural sac.[118] It is interesting to note that meningeal enhancement slowly decreases, even after the patient improves with treatment, and may take three–five months to resolve the meningeal changes.

Radionuclide cisternography (RC) was once considered the confirmatory test in the diagnosis of SIH. The presence of SIH is indirectly proven by the lack of ascent of the injected dye, rapid disappearance of the radioisotope from the CSF (within 4 h), and the early appearance of the radioisotope in the urinary bladder. However, leak sites have often not been demonstrated using cisternography. This is because the patient was brought back to the radiology department after injection of the radioisotope, and images were taken at several time intervals. Hence, leakage of the radioisotope may have occurred between the images. Other disadvantages of RC include poor spatial resolution, invasiveness, and possible radioisotope extravasation through the needle tract, resulting in inaccurate interpretation. For these reasons, RC is now considered to have limited usefulness in the diagnosis of SIH.[119,120]

CT myelography (CTM) and intrathecal gadolinium magnetic resonance myelography (Gd-MRM) can localize spinal CSF leaks.

• **Figure 39.6** Brain magnetic resonance findings consistent with intracranial hypotension. (A) Axial T2-weighted fluid-attenuated inversion recovery image demonstrating pachymeningeal thickening *(arrow)* and distension of the superior sagittal sinus *(arrowhead)*. Axial (B) and coronal (C) T1-weighted images after gadolinium contrast demonstrating diffuse smooth pachymeningeal enhancement *(arrow)* and distension of the superior sagittal and transverse sinuses *(arrowheads)*. (D) Sagittal T1-weighted image demonstrating signs of brain descent *(sagging):* effacement of the interpeduncular cistern *(dotted ellipse),* enlargement of the pituitary gland *(dotted arrow),* depression of the corpus callosum *(curved arrow),* inferior pointing of the splenium of the corpus callosum *(asterisk)*. Williams EC, Buchbinder BR, Ahmed S, Alston TA, Rathmell JP, Wang J. Spontaneous intracranial hypotension: presentation, diagnosis, and treatment. *Anesthesiology.* 2014;121(6):1327–1333. Reprinted with permission.

CTM is now considered the diagnostic procedure of choice to show the location and extent of CSF leak in SIH.[101] It has better localizing power and provides finer details compared to RC. Standard CTM is used to localize slow CSF leaks wherein the CSF is confined to one or two vertebral levels, while dynamic CTM (D-CTM), whereby the contrast is injected intermittently followed by immediate scanning after each injection, is utilized when the leak is suspected to be rapid and spread over several vertebral levels.[121] D-CTM involves placement of the patient on a tilt table, thereby facilitating contrast flow over the dependent segment of the thecal sac where the suspected leak is located (i.e. prone positioning for the ventral leak). Because patients are positioned on a tilt table, D-CTM requires considerable patient cooperation and limits the scope of imaging, precluding visualization of the entire spine.[122,123] Gd-MRM has higher sensitivity than CTM for small, slow leaks but is more complex to perform.[120,124] Intrathecal gadolinium administration is considered off-label, and doses should not exceed 0.3–0.5 mL because of increased risk of acute neurotoxicity and potential fatal encephalopathy.[125] In cases of rapid CSF leaks or recalcitrant SIH symptoms with negative imaging, digital subtraction myelography can be employed as an adjunctive test.[126]

The location of the CSF leak can be anywhere throughout the spine, with the cervicothoracic and thoracolumbar junctions serving as the most common sites.

Treatment of SIH

Many patients respond to conservative measures alone, including bed rest, oral hydration, steroids, oral or intravenous caffeine, and the application of an abdominal binder. An EBP is considered when conservative treatment fails because it can induce an inflammatory reaction to seal the leak. It is the treatment of choice for SIH, although it is less effective in SIH than in postdural puncture headaches. The lower success rate may be related to the injection of the blood away from the site of CSF leak, the presence of multiple CSF leaks, and the rare occurrence of CSF leaks at the anterior aspect of the spinal cord or nerve root sleeves.

In the absence of CTM demonstrating the exact location of CSF leak, most pain medicine practitioners inject the blood at the thoracolumbar area to cover the upper and lower thoracic levels. If not effective, a second injection can be considered in the lumbar region. Ferrante et al.[127] reported excellent results with blind lumbar EBPs in 42 patients by strictly maintaining the Trendelenburg position immediately before and 24 h after EBP, premedicating with acetazolamide, and activity modification for two weeks post-procedure. The prolonged Trendelenburg position promotes the rostral spread of the EBP; maintaining this position for 24 h after the procedure is probably not necessary. Debate exists over the superiority of targeted EBP. In 56 patients with SIH, 87% of patients exhibited benefit after just one targeted EBP vs. 52% of patients in the blind EBP group.[128] However, in a retrospective review of 116 patients who underwent EBP for SIH, no clinical difference was observed between the targeted vs. two-site blind EBP groups.[129] Factors associated with greater first blood patch efficacy included volume of blood, number of levels injected, and targeted injections.[130] Performing more than two EBPs is probably not necessary. If one or two EBPs are not effective, then a CTM should be performed before another EBP is attempted to delineate the vertebral level and the site of CSF leak.[131] The use of a transforaminal epidural blood patch, although reported to be successful,[132] should be done as a last resort. This is because of possible compression/occlusion of the radicular artery accompanying the nerve root, leading to segmental ischemia of the spinal cord and possible paralysis.[133]

Epidural patches performed with fibrin glue alone[34] or autologous blood have been described.[135] It should be noted that fibrin glue has been associated with allergic reactions and viral infections. Surgical intervention is warranted if multiple EBPs are ineffective,[136,137] and the patient's condition deteriorates.[101,109] Surgery for SIH is challenging, and close follow up is recommended because some patients may develop recurrent CSF leaks.

The recurrence of headaches after successful treatment may be due to leak recurrence. If the character of the headache changes, rebound transient intracranial hypertension[138] and dural venous sinus thrombosis are possible.[139]

SIH Summary

SIH is characterized by the same symptoms as PDPH, although the patient had no history of meningeal puncture. CSF pressure is usually low on diagnostic lumbar puncture, and there is meningeal enhancement on MRI. CTM confirms the diagnosis and helps determine the exact site of CSF leak. If conservative measures are ineffective, several EBPs may be required to treat the headache.

Key Points

Cervicogenic Headache

- Cervicogenic headache pain refers to pain referred to the cervical spine from the neck.
- The pathogenesis can be explained by the overlap between the first three cervical nerves, the trigeminal nucleus, and the cervical plexus.
- Cervicogenic headaches can be diagnosed based on clinical symptoms that meet the criteria or diagnostic block.
- It is very important to distinguish cervicogenic headaches from internal carotid or vertebral artery dissection, tumors in the posterior fossa, Arnold Chiari formation, migraines, and tension-type headaches.
- A full history and physical examination are necessary for diagnosis. History may include a history of whiplash injury or cervical disease. Physical examination should include the range of motion of the neck.
- Imaging can be used to determine the presence of cervical disease. However, a temporal relationship is required to prove causation.
- Treatment can be non-pharmacologic, including massage, physical therapy, transcutaneous electrical nerve stimulation therapy, and psychotherapy.
- Interventional treatments such as radiofrequency ablation can be curative in patients who have complete pain relief after a diagnostic block.
- Surgical intervention, such as neurectomy and dorsal rhizotomy, requires weighing the risk of worsening pain post-intervention with the possible benefits of the procedure.

Post-meningeal Puncture Headache

- The crucial components of PMPH are a history of dural/arachnoid puncture and bilateral postural headaches.
- Headache after dural/arachnoid puncture is not directly related to the amount of CSF leakage or subarachnoid pressure. Headache may be secondary to a sudden alteration in CSF volume and subsequent cerebral vasodilatation.
- Concomitant intracranial pathologies may be present in patients with PMPH. The signs and symptoms of alternative pathology include the presence of a significant nonpostural component of the headache, a changing pattern of the headache, and severe nausea and vomiting.
- Prevention of PMPH depends mainly on needle size and needle tip design. The smallest practical needle diameter with a non-cutting tip was associated with the lowest risk of PMPH.
- Initial therapy for PMPH, in the first 24 h, should be conservative, relying mainly on medications. Approximately 85% of PMPHs resolve spontaneously within five days.
- The initial and rapid relief from an EBP is secondary to the circumferential compression of the dura and reduction of the intradural volume. This shifting of the vertebral subarachnoid CSF cephalad causes re-suspension of the cerebral structures, reduction of traction on pain-sensitive intracranial structures, and decreased cerebral vasodilatation. The lasting relief from an EBP is related to the sealing of the dural/arachnoid hole.
- Caffeine and theophylline block the brain adenosine receptors, causing cerebral vasoconstriction. The acute increase in subarachnoid pressure after EBP may deactivate adenosine receptors and relieve headaches.
- Prevention of PMPH with pharmacologic agents or prophylactic EBP after ADP has not been proven effective.
- Sphenopalatine ganglion blocks may be considered a safe and effective alternative to EBP.

SIH

- SIH is characterized by symptoms similar to meningeal puncture headache in a patient with no history of meningeal puncture.
- The cause of SIH is leakage of the CSF due to weakness of the spinal meninges, such as meningeal diverticulum, or small tears in the root sleeves or cysts. Other associated anatomical abnormalities include herniated discs and vertebral spurs.
- The hallmarks of SIH include postural headache (without a previous history of dural puncture), low CSF pressure on diagnostic lumbar puncture, and meningeal enhancement on MRI.
- The symptoms include postural headaches, neck stiffness, visual, hearing, balance disturbances, back pain, and radiculopathy.
- Although the headache is classically postural, it can be nonpositional or intermittent. It can be gradual or sudden at the onset.
- CT myelography (CTM) is the diagnostic procedure of choice in SIH because it has a better chance of showing the location of the CSF leak and provides finer details than RC.
- Gadolinium magnetic resonance myelography (Gd-MRM) is more sensitive than CTM but is also more complex to perform. However, intrathecal injection of gadolinium is contraindicated because of recent reports of encephalopathy and death from unintentional intrathecal injection of gadolinium.
- EBP is the treatment of choice for SIH, and several EBPs may be required if there are multiple sites of leakage.
- Although fibrin glue can be injected into the epidural space, there are not enough publications or experience to support its routine use.
- If conservative measures and EBPs are ineffective, surgical repair can be employed if structural abnormalities or focal CSF leaks are identified.

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40

Orofacial Pain

AURELIO ALONSO, MASSIMILIANO DIGIOSIA, DANIELA VIVALDI

Introduction

Orofacial pain (OFP) refers to pain associated with the face, head, and neck and can be associated with the masticatory and cervical muscles, temporomandibular joint, intraoral tissues, salivary glands, and others.[1,2] It can be classified into the following categories: musculoskeletal, neurovascular, and neuropathic orofacial pain conditions.

Orofacial pain disorders have complex anatomy and specialized sensory innervations of the head and neck. Many orofacial pain disorders are unique and represent a clinical diagnostic challenge. Patients may present with one entity to multiple types of orofacial pain. This chapter presents an introduction to practical issues regarding assessment, diagnosis, and management of common orofacial pain disorders.

Other forms of orofacial pain, such as odontogenic pain, will not be discussed in this chapter since these conditions are usually already ruled out by a general dentist or other dental specialist.

The specialized structures of the head and face have a rich sensory innervation supplied by the trigeminal system, lower cranial nerves, and upper cervical roots. Pain is one of the most prominent symptoms of disease in this area. Usually, the acute pain symptoms closely correlate with other signs and symptoms of the disease. However, the correlation between pain and other symptoms may not be evident in several more complex, chronic pain problems, particularly those involving the masticatory system.[3]

Epidemiology of Orofacial Pain

Chronic pain affects approximately 100 million adults in the United States, with an economic burden of over 600 billion.[4] OFP is one of the most common pain conditions; its prevalence is estimated to be between 17%–26% in the general population, and 22% of the population suffered at least one orofacial pain in the length of six months.[2,5] Similar to other pain conditions, OFP is more prevalent in females than males.[6,7] After toothache, temporomandibular disorder (TMD) is the most common orofacial pain.[5] In a large prospective multi-site study, the incidence of TMD was 3.9% annually, and females had only slightly higher incidence than males.[8] The onset and chronification of TMD are associated with other comorbid pain conditions like chronic wide spread pain, lower back pain, and headaches (Fig. 40.1).[9–14] The prevalence of TMD depends on the illness in question, the diagnostic criteria used to identify the disease, and the study population. For example, in a review study that used the Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TMD) as the diagnostic criteria for TMD, the general population prevalence of temporomandibular joint (TMJ) pain was 2.6%, muscle disorders had a prevalence of 9.7%, in comparison, the prevalence of these conditions in the patient population was 45.3% and 30.1%, respectively.[15,16] Unlike TMD that has a recognized and validated diagnostic criteria in the RDC/TMD and Diagnostic Criteria for Temporomandibular Disorder (DC/TMD),[15,17] the prevalence and incidence of several OFP conditions, for example, neurovascular orofacial pain, are unknown because until recently they were not defined in a comprehensive, internationally acceptable comprehensive classification.[18,19]

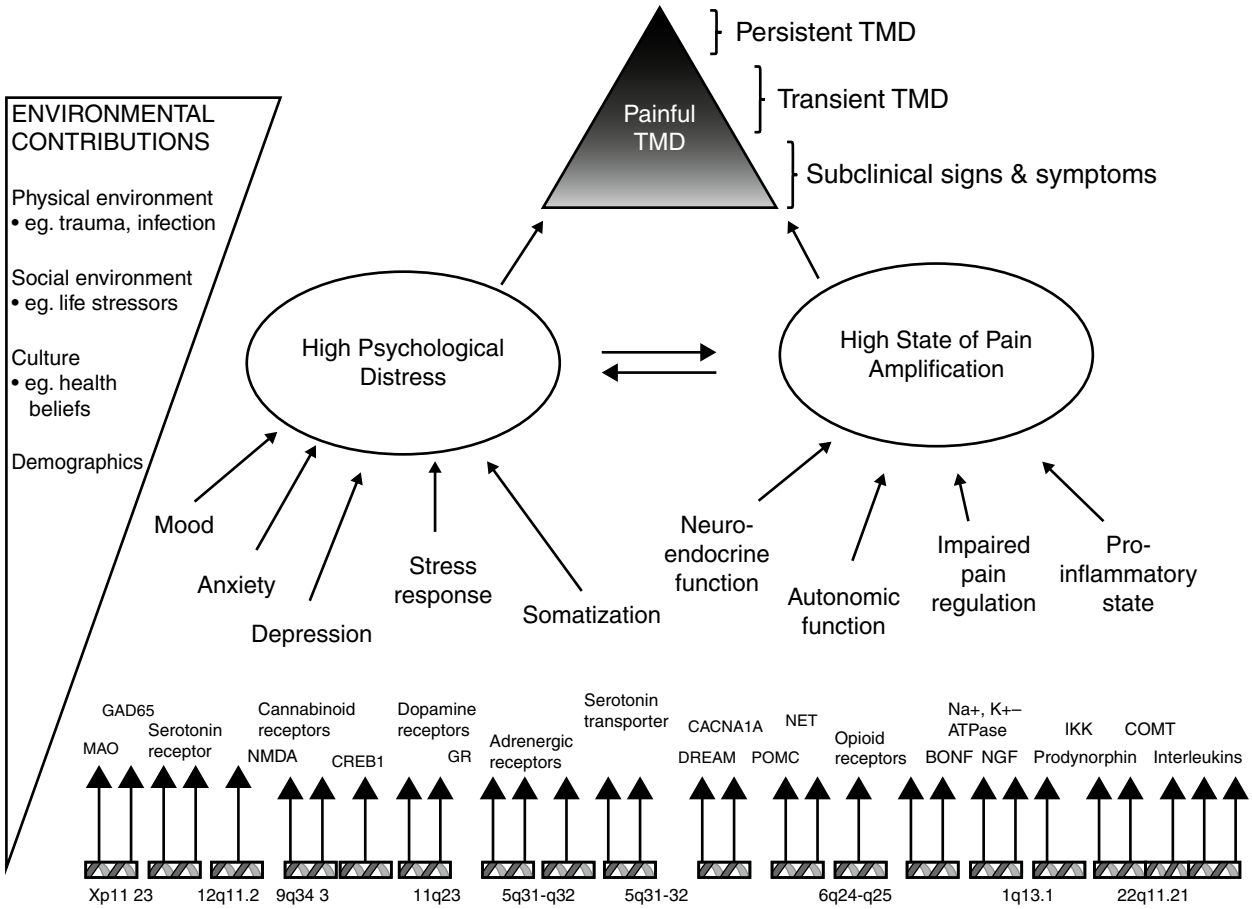
Orofacial Pain Classification

Several classifications have been developed over the years to better categorize the types of OFP. These classifications include the International Classification of Headache Disorders (ICHD-3)[20] and the International Classification of Orofacial Pain (ICOP).[18] Despite the fact these two classifications include TMD, a more specific classification for TMD was developed to assist researchers and clinicians, the first one was developed in 1992, RDC/TMD,[15] and in 2014, DC/TMD.[17] A summary of orofacial pain classifications is shown in Figure 40.2.

Temporomandibular Disorders

TMDs are defined as a subgroup of orofacial pain that involves the TMJ, masticatory muscles, and associated head and neck musculoskeletal structures.[1]

Patients with TMD most frequently present with pain, limited or asymmetric mandibular range of motion, and TMJ sounds.[21,22] The pain or discomfort is often localized to the jaw, TMJ, and muscles of mastication, and cervical muscles are commonly involved. Commonly associated symptoms include ear pain and stuffiness, tinnitus, dizziness, neck pain, and headache. In some cases, the onset is acute, and symptoms are mild and self-limiting. However, about 15% of patients will develop chronic TMD,[23] with persistent pain in association with physical, behavioral, psychological, and psychosocial symptoms similar to those of patients with chronic pain syndromes in other areas of the body (e.g. arthritis, low back pain, chronic headache, fibromyalgia, chronic regional pain syndrome, irritable bowel syndrome),[24–26] all requiring a coordinated interdisciplinary diagnostic and treatment approach.



• **Figure 40.1** This model displays two principal intermediate phenotypes (psychological distress and pain amplification) that contribute to the onset and persistence of temporomandibular disorder (TMD). Each intermediate phenotype represents a constellation of more specific risk factors, all of which are subject to genetic regulation. Interactions between intermediate phenotypes occur in the presence of environmental contributions that further contribute to the onset and persistence of painful TMD. Time is not shown in the model because its effects occur implicitly on a third dimension not readily shown in the diagram. Reproduced with permission from Maixner W, et al. 2011.[29]

Etiology

In 1934, Costen, an otolaryngologist, evaluated 13 patients who presented with pain in or near the ear, tinnitus, dizziness, a sensation of ear fullness, and difficulty swallowing.[27] He observed that these patients had many missing teeth and, as a result, their mandibles were over closed. The patients seemed to improve when their missing teeth were replaced, and the proper vertical dimension of the occlusion was restored. The malocclusion and improper jaw position were perceived to be the cause both of "disturbed function of the TMJ" and the associated facial pain. The emphasis of treatment was on altering the affected patient's occlusion.

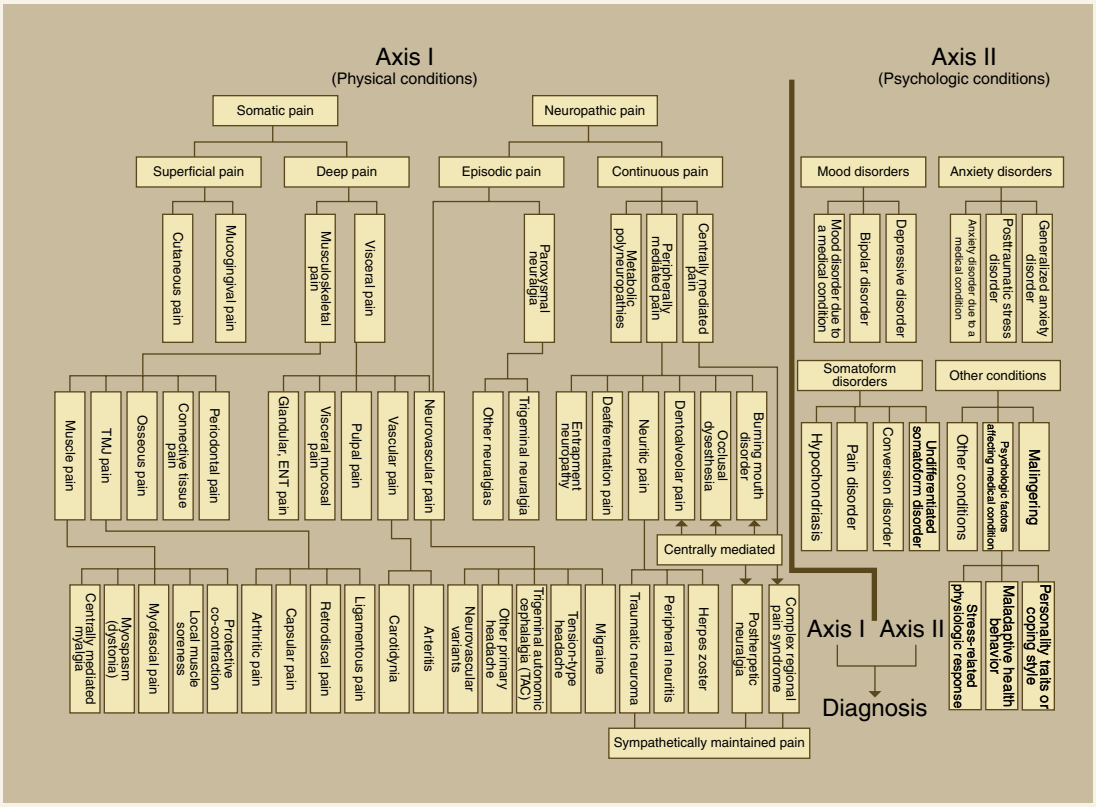
More recently, advances in the understanding of joint biomechanics, neuromuscular physiology, autoimmune, musculoskeletal disorders, and pain mechanisms have resulted in changing concepts of the etiology of TMDs. These disorders are now considered multifactorial in etiology, with biologic, behavioral, environmental, social, emotional, and cognitive factors alone or in combination contributing to the development of signs and symptoms of TMDs (Fig. 40.1).[1,22,28,29]

Various forms of trauma to the TMJ structures (ligaments, articular cartilage, articular disc, bone) can lead to intraarticular biochemical alterations that have been demonstrated to produce oxidative stress and the generation of free-radicals. Subsequent inflammatory changes in synovial fluid with the production of a variety of pro-inflammatory cytokines can then lead to alteration in the functioning of normal tissues and degenerative disease in the TMJ.[30–34]

Genetic marker studies involving catecholamine metabolism and adrenergic receptors suggest that certain gene polymorphisms (e.g. in the catechol-O-methyl transferase gene) might be associated with changes seen in pain responsiveness and pain processing in patients with chronic TMDs.[35–37]

Differences in pain modulation have been reported between women and men with TMDs; women have been observed to demonstrate decreased thresholds to noxious stimuli and more hyperalgesia. In addition, in women with TMDs, some studies suggest that the affective component of pain may be enhanced during the low-estrogen phase of the menstrual cycle.[38–40]

Functional brain imaging studies demonstrating changes in cortical circuitry support the concept that TMDs are very similar to other chronic pain disorders and may be related to abnormal pain processing in the trigeminal system.[41–43] In particular, muscle pain disorders appear to have little, if any, abnormality of the muscles or peripheral tissues and may represent a central sensitization pain producing process. Because of the central sensitization, TMD was classified among other chronic painful disorders as part of the chronic overlapping pain conditions.[44]



• **Figure 40.2** Classification of facial pains. With permission from Dr. Okeson from *Bell's Orofacial Pain.* Quintessence; 2014.

Lastly, numerous bio-behavioral studies support a connection between chronic TMDs and comorbid psychopathology (anxiety and depression disorders, posttraumatic stress disorder, and childhood physical, sexual, and psychological abuse).[45–51] TMDs fall in the 11th major category of the International Headache Society's (ICHD-3) classification.[20] However, most researchers use the RDC/TMD or DC TMD for diagnosis purposes.[15,52]

Temporomandibular Joint Disorders (TMJD)

The TMJ is a ginglymoarthrodial synovial joint capable of rotational and translational movements. A bilateral joint (a single bone—the jaw—with a right and left joint) cannot function separately. What affects one joint also influences the other. It is formed by the articulation of the mandibular condyle with the glenoid fossa/articular eminence of the temporal bone.

The articular surfaces of the condyle and glenoid fossa/articular eminence are covered with fibrocartilage rather than hyaline cartilage, as in other synovial joints except for the clavicle. Fibrocartilage can resist heavy loads and has unique healing and adaptive properties.[53]

An articular disc, made of fibrocartilage, is interposed between the condyle and the glenoid fossa. The disc has a biconcave shape; thicker in its anterior (2 mm) and posterior (3 mm) portions and thinner in the middle. It acts as a "cushion" to absorb stress, distribute loads, and facilitate jaw movements.

The disc divides each TMJ into two articular joint spaces: upper and lower joint space. The rotational movement happens mainly in the inferior joint space, between the condyle and the inferior surface of the disc. The translational movement in the upper joint space, between the upper surface of the disc and the glenoid fossa/articular eminence.[54,55]

The most common TMJ disorders are:[56]

Joint pain (arthralgia, arthritis)
Joint disorders (internal derangement or disc-condyle disorders)
Joint diseases (degenerative joint disease [DJD]: osteoarthrosis and osteoarthritis)

Joint Pain

Joint pain is characterized by localized pain exacerbated by function, parafunction, and provocation.

Arthralgia

According to the DC/TMD,[57] arthralgia is defined as pain of joint origin affected by jaw movement, function, or parafunction, and the replication of the pain occurs during provocation testing of the TMJ.

History has to be positive for both:

1. pain in the jaw, temple, ear, or in front of the ear AND
2. pain modified with jaw movement, function, or parafunction

The clinical examination has to be positive for both:

1. confirmation of pain location in the area of the TMJ(s)
2. report of familiar pain in the TMJ with at least one provocation test:
   - palpation of the lateral pole (0.5 kg pressure) or around the lateral pole (1 kg pressure) OR
   - maximum unassisted or assisted opening, right or left lateral movements, or protrusive movements

Arthritis

Defined as pain of joint origin with clinical characteristics of inflammation or infection: edema, erythema, and/or increased temperature. It may result from trauma. In case of severe unilateral intraarticular swelling or effusion, it could be associated with occlusal changes such as ipsilateral posterior open bite. It is a localized condition, and there should not be a history of systemic inflammatory disease.[58]

History has to be positive for both:

- arthralgia AND
  1. swelling, redness, and/or increased temperature in front of the ear OR
  2. dental occlusal changes (posterior open bite) resulting from intraarticular inflammatory exudate

Clinical examination has to be positive for both:

- arthralgia AND
  - presence of edema, erythema, and/or increased temperature over the joint OR
  - reduction in dental occlusal contacts noted between two consecutive measurements

The patient has to be negative for rheumatologic disease, including those in systemic arthritis, and the pain is not better accounted for by another pain diagnosis.

Joint Disorders

Internal derangement (or disc- condyle complex disorders) is defined as an "abnormal relationship of the articular disc to the mandibular condyle, glenoid fossa and articular eminence, interfering with the smooth movements of the joint."[59] It is a localized mechanical disorder within the joint. The term is often used as a synonym for disc displacement.

The clinical manifestations of internal derangements are clicking joint, intermittent locking, limited mouth opening (closed lock), and open lock.

The DC/TMD includes several forms of internal derangement:

- Disc displacement with reduction
- Disc displacement with reduction with intermittent locking
- Disc displacement without reduction with limited opening
- Disc displacement without reduction without limited opening

Disc Displacement With Reduction

Disc displacements are usually anterior or anteromedial, although posterior and lateral displacements have been described in the literature. This may be partly related to the thinnest discal attachments being on the lateral pole of the condyle and the medial direction of pull by the lateral pterygoid and inward direction of condylar movement during mouth opening. Therefore disc displacement clinically suggests torn or stretched collateral discal ligaments that bind the disc to the condyle.

In disc displacement with reduction, clicking sounds on mouth opening and closing may be present**.** The term reduction is used to describe the misaligned disc temporarily coming back (or slipping back) to its proper interposition between the condyle and articular eminence/fossa during full opening (Fig. 40.3). On closing the mouth, the disc again displaces as the teeth come closer together. This repetitive, ongoing displacement on opening and closing produces a reciprocal noise (clicks) and is hence termed reciprocal clicking (Fig. 40.4). This stage may actually represent a physiologic accommodative stage without the need for therapy other than discussion regarding its anatomic significance.[60]

History has to be positive for at least one of:

1. in the last 30 days, any TMJ noise present with jaw movement or function OR
2. patient report of any noise present during the exam

The clinical exam has to be positive for at least one:

1. clicking, popping, and/or snapping noise during both opening and closing movements, detected with palpation during at least one of three repetitions of jaw opening and closing movements OR
2. clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of opening or closing movements AND
3. clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of right or left lateral or protrusive movements.

Imaging is the reference standard, and when this diagnosis needs to be confirmed with TMJ magnetic resonance imaging (MRI):

1. in the maximum intercuspal position, the posterior band of the disc is located anterior to the 11:30 position, and the intermediate zone of the disc is anterior to the condylar head AND
2. on full opening, the intermediate zone of the disc is located between the condylar head and the articular eminence.

Disc Displacement With Reduction With Intermittent Locking

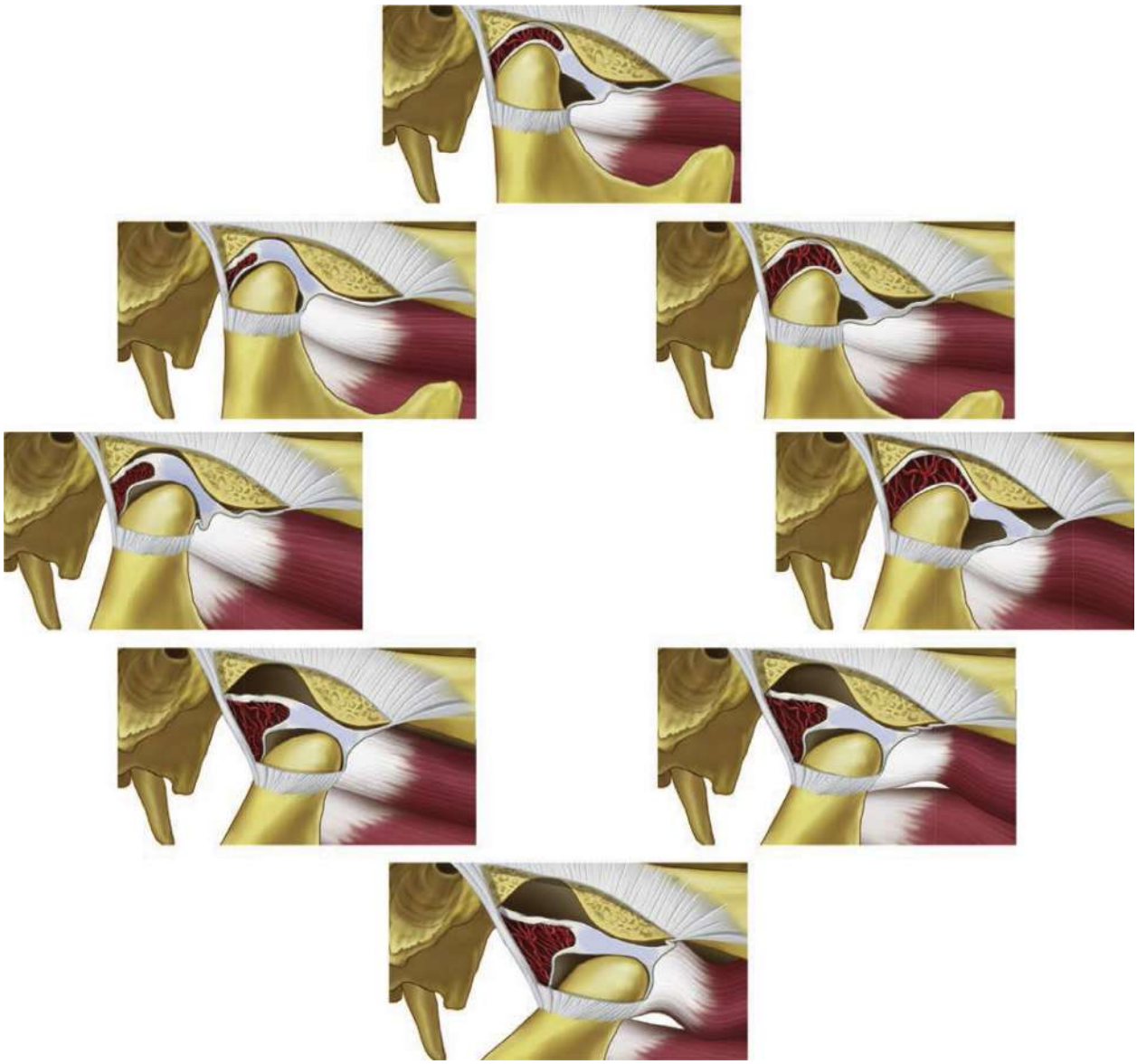
In this intracapsular disorder, the disc does not reduce during mouth opening, causing intermittent, limited mandibular opening. Usually, the patient can unlock the joint.

History has to be positive for:

1. in the last 30 days, any TMJ noise present with jaw movement or function OR
2. patient report of any noise present during the exam AND
3. in the last 30 days, jaw locks with limited mouth opening, even for a moment, and then unlocks.

The clinical exam has to be positive for at least one of:

1. clicking, popping, and/or snapping noise detected during both opening and closing movements, detected with palpation during at least one of three repetitions of jaw opening and closing movements OR



• **Figure 40.3** Disc displacement with reduction. Note that during opening, the condyle passes over the posterior border of the disc onto the intermediate area of the disc, thus reducing the anteriorly displaced disc. This discal movement can lead to momentary mechanical catching or locking. When this is present, the condition is called disc displacement with intermittent locking. With permission from Dr. Okeson.

2. clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of right or left lateral or protrusive movements

When this diagnosis needs to be confirmed, the imaging analysis criteria are the same as for disc displacement with a reduction.

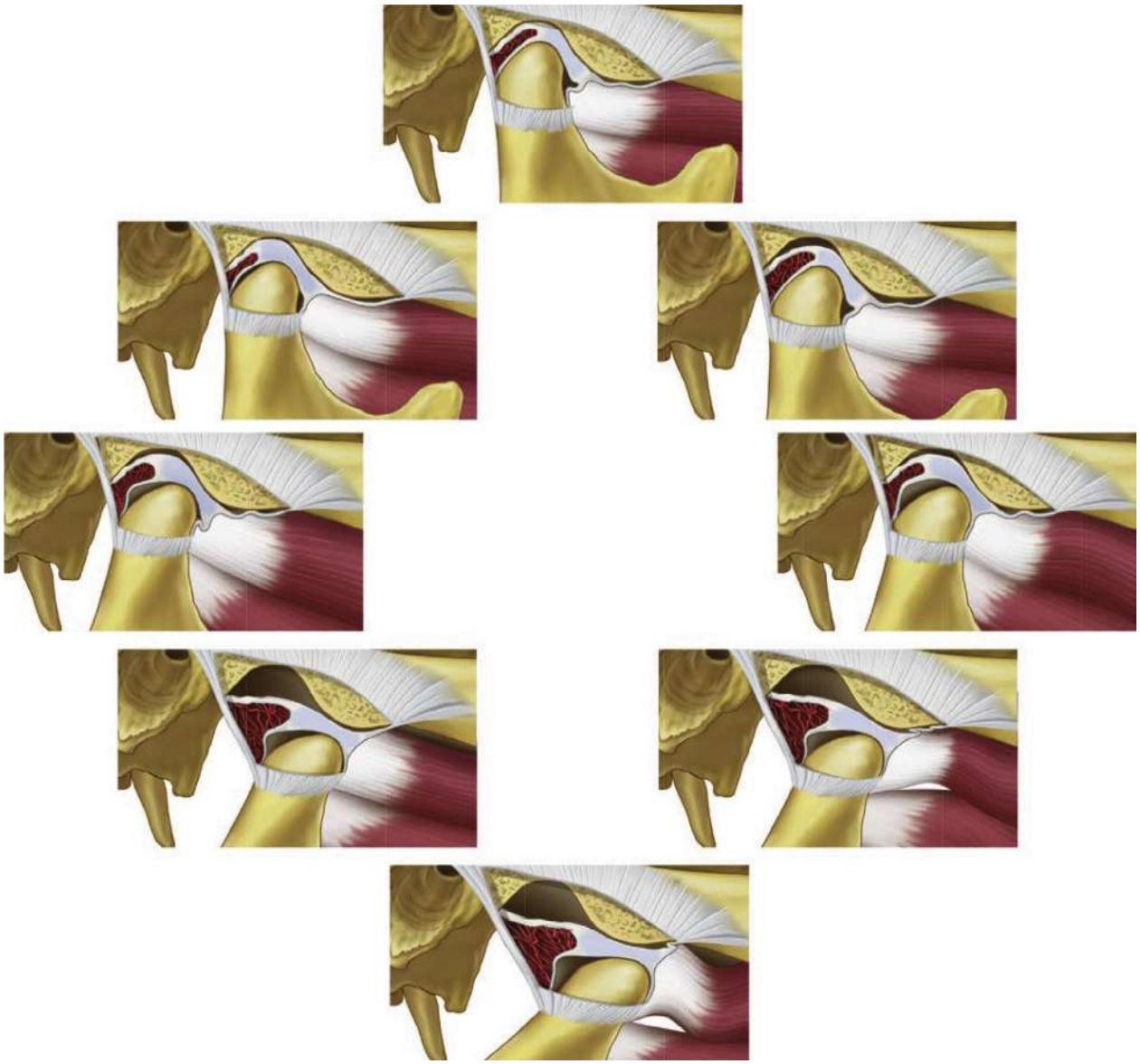
Disc Displacement Without Reduction With Limited Opening

Disc displacement without reduction is sometimes called a "closed lock." This suggests that the disc has been permanently displaced, and the disc's shape has been permanently changed such that it physically prevents the condyle of the mandible from translating to a fully open position (Fig. 40.5). There is a limitation of jaw opening to 22 to 25 mm with pain and a deflection of the mandible to the side of the lock. There is a reduction in the chewing capability because of pain, inflammation at the affected joint, and possible changes in the normal occlusion or "bite." An MRI of the TMJ is the "gold standard" to assess soft tissue details of the articular disc and its displacement, while hard tissue CBCT scans are generally done to assess chronic osteoarthritic or bony changes.[61,62] Considering its positive natural course, treatment should be reserved for painful symptomatic cases, and it should always be conservative (see the section on treatment). The goal of the treatment is the management of pain and improvement in mouth opening.[63,64]

History has to be positive for both:

1. jaw locked so that the mouth would not open all the way AND
2. limitation in jaw opening severe enough to limit jaw opening and interfere with the ability to eat

The clinical exam has to be positive for:



• **Figure 40.4** Disc displacement with a reciprocal clicking. Between positions two and three, a click is felt as the condyle moves across the posterior border of the disc. Normal condyle disc function occurs during the remaining opening and closing movement until the closed joint position is approached. Then a second click is heard as the condyle. With permission from Dr. Okeson.

Maximum assisted opening (passive stretch) movement including vertical incisal overlap <40 mm

When this diagnosis needs to be confirmed, the TMJ MRI criteria are positive for both:

1. in the maximum intercuspal position, the posterior band of the disc is located anterior to the 11.30 position, and the intermediate zone of the disc is anterior to the condylar head AND
2. on full opening, the intermediate zone of the disc is located anterior to the condylar head

Disc Displacement Without Reduction Without Limited Opening

The disc is still permanently displaced in this condition, but the clinical presentation is different: pain is often absent, and there is a restoration of function with normal maximum mouth opening.[65]

History has to be positive for both in the past:

1. jaw locked so that the mouth would not open all the way AND
2. limitation in jaw opening severe enough to limit jaw opening and interfere with the ability to eat

The clinical exam has to be positive for:

Maximum assisted opening (passive stretch) movement including vertical incisal overlap >40 mm

When this diagnosis needs to be confirmed, TMJ MRI criteria are the same as for disc displacement without reduction with limited opening.

Degenerative Joint Disease

In the DC/TMD classification, DJD is defined as a degenerative disorder involving the joint characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence.[6] DJD can result in dental

• **Figure 40.5** Disc displacement without reduction (closed lock). Note that the condyle never assumes a normal relationship on the disc but instead causes the disc to be maintained in front of the condyle. This condition limits the distance it can translate forward. With permission from Dr. Okeson.

malocclusions, including an anterior open bite, especially when present bilaterally or contralateral posterior open bite when present unilaterally.

DJD can be subclassified in:

- Osteoarthrosis (DJD without arthralgia)
- Osteoarthritis (DJD with arthralgia)

Osteoarthrosis

History has to be positive for at least one of:

- in the last 30 days, any TMJ noise present with jaw movement or function OR
- patient report of any noise present during the exam

The clinical exam has to be positive for:

- crepitus detected with palpation during maximum unassisted opening, maximum assisted opening, lateral or protrusive movements

If imaging is needed to confirm the diagnosis, TMJ CT/CBCT criteria are positive at least for one of:

- subchondral cyst, erosion, generalized sclerosis, osteophyte.

Osteoarthritis

History has to be positive for both:

- in the last 30 days, any TMJ noise present with jaw movement or function OR
- patient report of any noise present during the exam AND
- arthralgia

Clinical examination has to be positive for both:

- crepitus detected with palpation during maximum unassisted opening, maximum assisted opening, right or left lateral movements or protrusive movements AND
- arthralgia

Imaging: same TMJ CT/CBCT criteria as for osteoarthrosis.

Systemic Arthritis

The TMJs can also be affected by systemic inflammatory conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis, infectious arthritis, Reiter's syndrome), and crystal induced disease (gout, chondrocalcinosis). TMJ can also be affected by connective tissue diseases such as scleroderma, Sjögren's syndrome, and lupus erythematosus. Condylar resorption, a consequence of inflammation, can be associated with severe dental malocclusion (anterior open bite).

The diagnosis and management of these conditions should always be done in collaboration with a rheumatologist.[58]

History has to be positive for both:

- rheumatologic diagnosis of a systemic inflammatory joint disease AND
- in the past month, any TMJ pain present OR
- TMJ pain that worsens with episodes/exacerbations of the systemic inflammatory joint disease.

Clinical examination has to be positive for arthritis or crepitus detected with palpation during maximum unassisted opening, maximum assisted opening, right or left lateral movements, or protrusive movements.

TMJ CT/CBCT or MRI is positive for at least one of subchondral cysts, erosions, generalized sclerosis, or osteophytes.

Idiopathic Condylar Resorption (ICR)

ICR is a severe form of joint degeneration that usually affects young female patients (also known as cheerleader syndrome). It is almost always bilateral, resulting in loss of condylar support, causing a severe anterior open bite (Fig. 40.6). The presence of pain or articular sounds is variable. The cause is unknown, but it has been suggested that it may be a severe form of DJD and that estrogen may be implicated.[58]

History has to be positive for progressive dental occlusal changes.

Clinical examination has to be positive for both:

1. anterior open bite AND
2. evidence of progressive dental occlusal change with at least one of:
   a. occlusal facets that cannot be approximated (indicating that teeth were touching before the occlusal changes) OR
   b. change in sequential dental occlusal measurement over time (overjet, overbite, intercuspal contacts)

Imaging has to be positive for one of:

1. CT/CBCT evidence of resorption of part or all of the condyle(s) OR
2. lateral cephalometric change with sequential imaging over time

The patient has to be negative for rheumatologic disease.

Neoplasm

Neoplasm of the joint may be benign (chondroma, osteochondroma) or malignant (primary or metastatic). They may present with the same signs and symptoms of TMD—pain during function, limited mouth opening, crepitus, occlusal changes—which could lead to misdiagnoses. Signs and symptoms suggestive of neoplasia are altered sensation (numbness, tingling, allodynia), motor dysfunction (abnormal or uncontrolled jaw and facial movements, paralysis), and recent visible changes (swelling, facial asymmetry).[66] Diagnostic imaging such as CT/CBCT and/or MRI are essential when a neoplasm is suspected.

Disorders of the Masticatory Muscles

It is believed that the cause of masticatory muscle disorders is overuse and ischemia of the muscles, leading to pain.[67–70] The most common masticatory muscle disorders are myalgia and myofascial pain. However, muscle spasms, masticatory muscle co-contraction, and tendinitis can also be present and be part of the TMD spectrum.

Prevalence of Muscles Disorders

Muscle pain disorders are the most common cause of persistent pain in the head and neck, and they affect about 50% of the population with chronic head and neck pain.[71] They also are a common cause of pain in the general population, with 20% to 50% having the disorder; about 6% have symptoms that are severe enough to warrant patient to seek for treatment.[72,73]

Etiologic Factors

Onset factors of masticatory muscle disorders include direct or indirect trauma (microtrauma and/or macrotrauma) to the masticatory muscles and repetitive strain and stress activities that overload the muscles.[1] Macrotrauma events include a direct blow to the jaw and opening the mouth too wide or for too long a period during activities, such as dental visits, eating, yawning, and sexual activity. In some cases, indirect trauma that is because of a whiplash-type of injury may initiate muscle pain.[74] Local infection and trauma may cause myositis and lead to muscle contracture if not resolved. Occupational and repetitive strain injury may cause myofascial pain and muscle spasm if acute. Sleep disturbance and nocturnal habits can also contribute to masticatory muscle pain.

Oral parafunctional habits, such as teeth clenching, jaw thrusting, gum chewing, and jaw tensing, can add repetitive strain to the masticatory muscles and cause tenderness and pain. Postural strain caused by a forward head posture, increased cervical or lumbar lordosis, some occlusal abnormalities, and poor positioning of the head or tongue have also been implicated in masticatory muscle disorders. Psychosocial stressors, such as relationship conflicts, monetary problems, feeling hurried or overscheduled, or poor pacing skills, can play an indirect role.

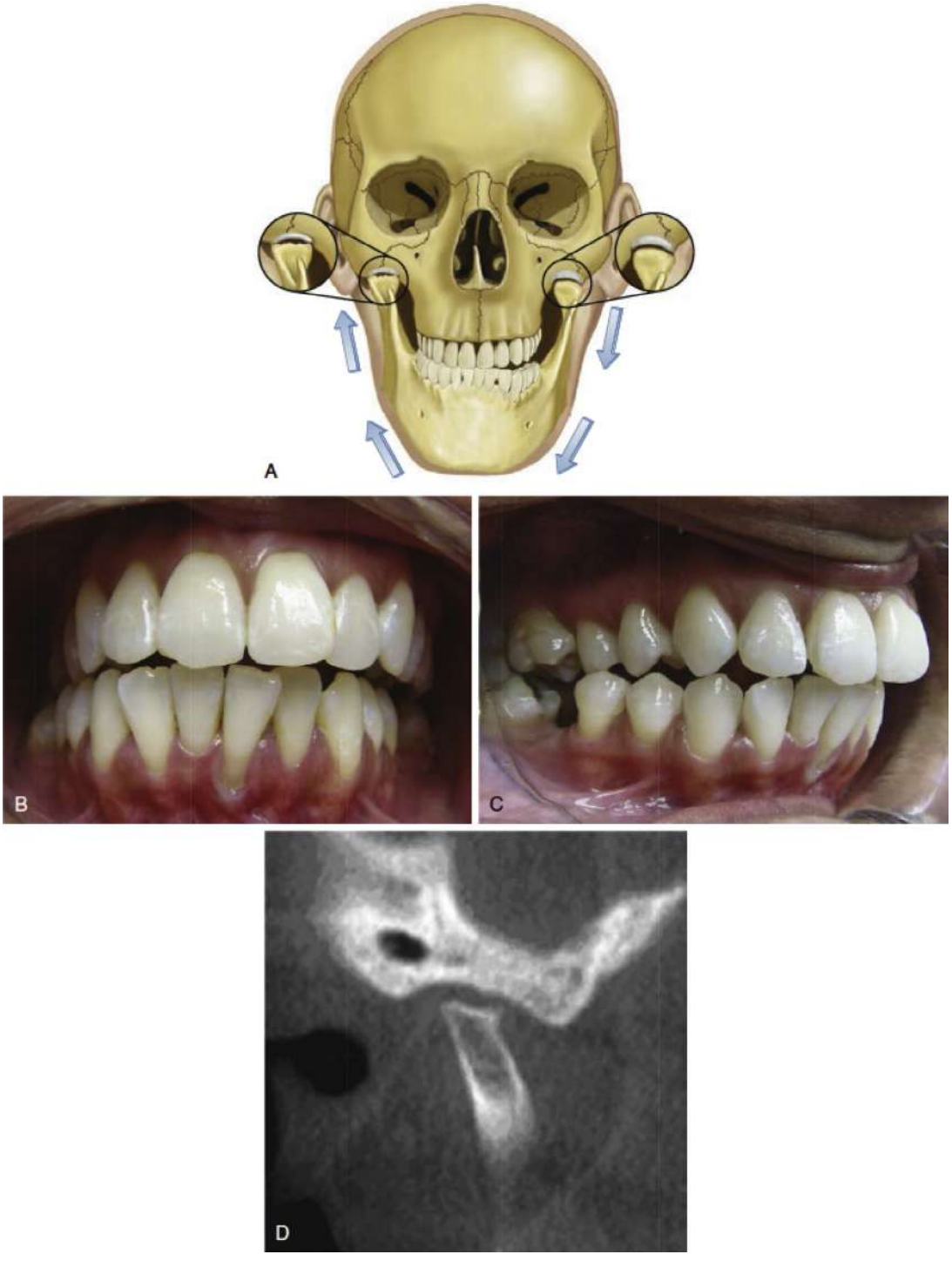
Pathophysiology and Mechanisms

Because there are no specific anatomic changes with muscle pain, no conclusive mechanisms are identified in cases of non-traumatic etiology. Thus several factors may explain the development and persistence of masticatory muscle pain.[1] Including the repetitive strain/stress, neurophysiologic, and central hypothesis.[75]

According to the Diagnostic Criteria for Temporomandibular Disorder (DC/TMD), the most common pain related TMD are myalgia and myofascial pain, and TMJD mentioned above. However, forms of muscle disorders can also be present in orofacial pain, such as muscle spasms and tendinitis.

Myalgia

Myalgia of the masticatory usually occurs with jaw function, parafunction habits (e.g. clenching teeth, chewing gum, biting nails, and others). It can also be elicited by the provocation of the muscles during muscle palpation, which will duplicate the patient's complaint.

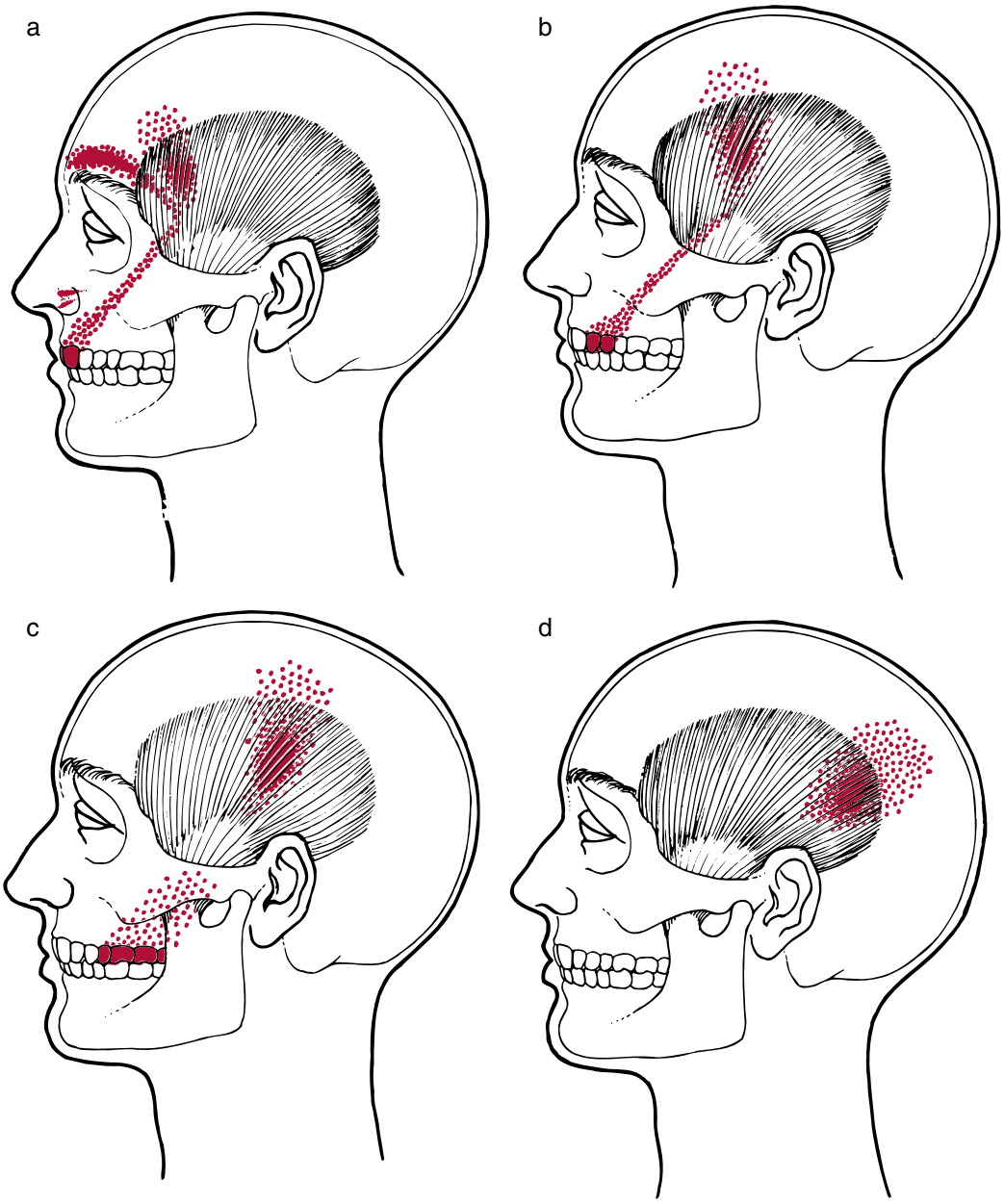


• **Figure 40.6 A,** Sometimes significant osteoarthritic changes occur in only one joint. When this occurs rapidly, the affected condyle collapses, resulting in a shifting of the mandible to that side. This is referred to as idiopathic condylar resorption. **B,** Note that for this patient, there has been a midline shift to the patient's right. This shift is even evident in the relationships of the posterior arches. This idiopathic condylar resorption was isolated to the patient's right condyle. **C,** The loss of condylar support in the right condyle caused a shift to the right, resulting in only the right second molar contacting. **D,** A cone-beam computed tomographic scan of the right condyle. Note the degenerative changes. With permission from Dr. Okeson.

According to the DC/TMD,[17] myalgia is a pain of a muscle origin affected by jaw movement, function, or parafunction and replication of this pain occurs with provocation testing of the masticatory muscles.

It has to be positive for both:

1. pain in the jaw and temple, in the ear, or in front of the ear, AND
2. pain modified with jaw movement, function, or parafunction



• **Figure 40.7A** Patterns of pain and tenderness referred from trigger points (TrPs) in the left temporalis muscle (essential zone solid red, spillover zone stippled). (a), referred pain from TrPs in the anterior portion of the temporalis muscle; (b and c), represent referred pain arising from TrPs in the middle portion of the temporalis muscle; (d), referred pain from TrPs in the posterior portion of the muscle. (From Donnelly JM: Travell, Simons and Simons' Myofascial Pain and Dysfunction. Third edition. Baltimore, MA: Williams & Wilkins, 2018.)

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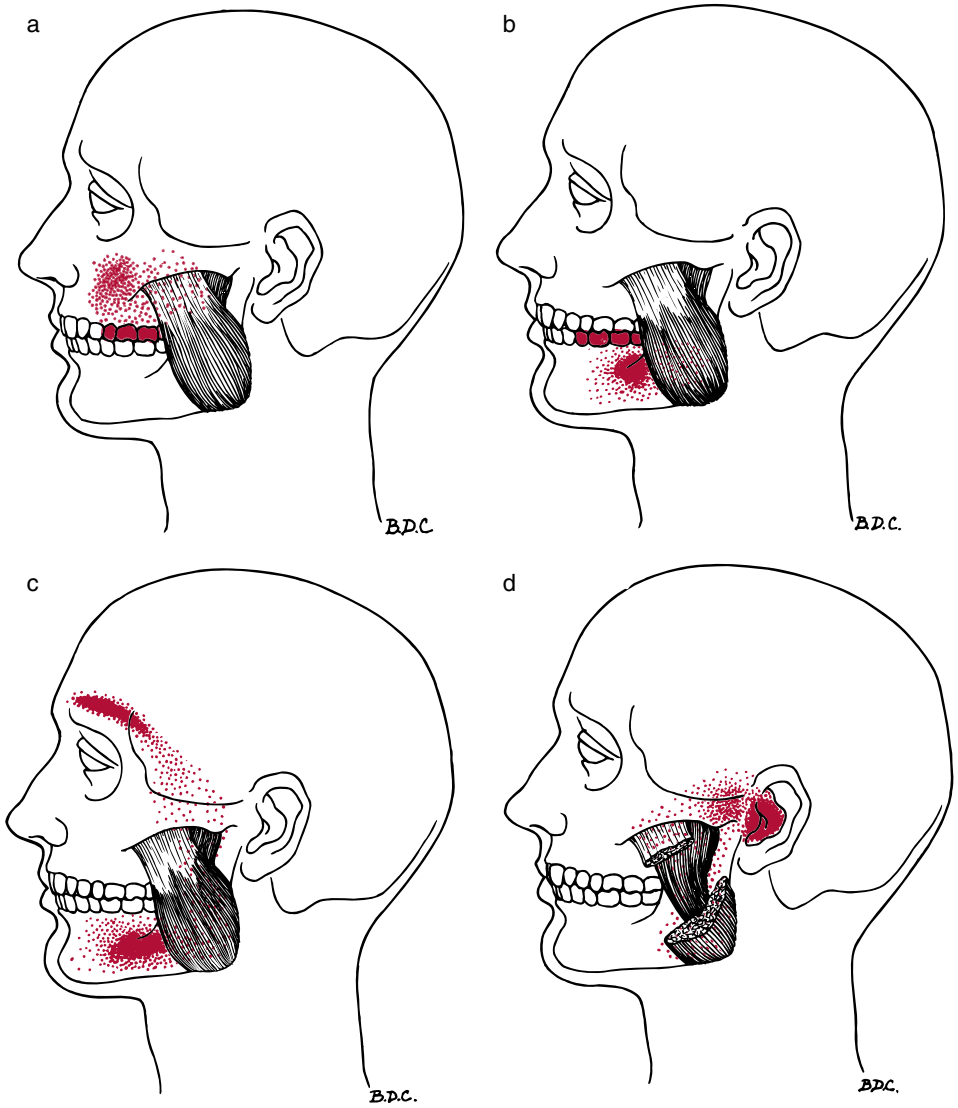
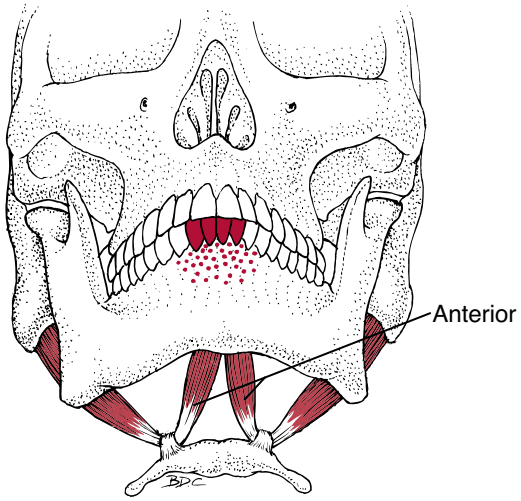


• **Figure 40.7B** Referred pain patterns arising from TrPs in the masseter muscle. Solid red shows essential referred pain zones, and the stippled areas are spillover pain zones. (a), Referral patterns from TrPs near the musculotendinous junction of the superficial layer, upper portion. (b), Referral patterns from TrPs in midmuscle of the superficial layer. (c), Referral patterns from TrPs of the lowest portion of the superficial layer, near its attachment. (d), Referral patterns from TrP in the upper posterior part of the deep layer below the temporomandibular joint. (From Donnelly JM: Travell, Simons and Simons' Myofascial Pain and Dysfunction. Third edition. Baltimore, MA: Williams & Wilkins, 2018.)



• **Figure 40.7C** Referred pain patterns of TrPs in the anterior belly of the digastric muscle. (From Donnelly JM: Travell, Simons and Simons' Myofascial Pain and Dysfunction. Third edition. Baltimore, MA: Williams & Wilkins, 2018.)

Positive for both:
1. confirmation of pain location (s) in the temporalis and masseter muscles AND
2. report of familiar pain in the temporalis or masseter muscles(s) with at least one provocation test:
   a. palpation of the temporalis or masseter muscles or
   b. maximum unassisted or assisted opening movements

For local myalgia pain with localization only at the site of palpation when using the myofascial examination protocol.[76]

Positive for both:
1. pain in the jaw, temple, in the ear, or in front of the ear; AND
2. pain modified with jaw movement, function, or parafunction

Positive for:
1. confirmation of pain locations in the temporalis or masseter muscles AND
2. report familiar pain with palpation of the temporalis and masseter muscles AND
3. report pain localized to the site palpation.

Myofascial Pain

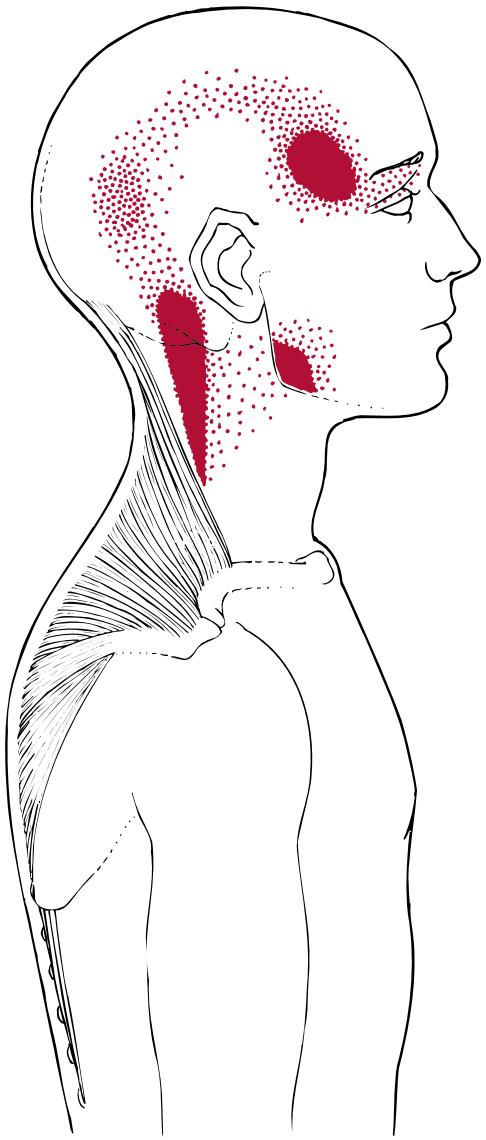
Myofascial pain is a regional muscle pain condition characterized by local areas of firm hypersensitive bands of muscle known as trigger points. Unfortunately, myofascial pain is overlooked and not well understood.[77] Good evidence suggest that myofascial pain originates from the CNS.[69,78] Some other etiologic factors area also known to be clinically present in myofascial pain such as protracted local muscle soreness, constant deep pain, increased emotional stress, sleep disturbance,[79,80] local factors and idiopathic trigger point mechanisms.[77]

Myofascial trigger points are also frequently overlooked and misunderstood sources of the distressingly ubiquitous musculoskeletal aches and pains of humankind. The sensory, motor and autonomic symptoms caused by myofascial trigger points add more challenges for its diagnoses. The specific muscle or muscle group that causes the symptoms should be identified by a trigger point in the muscle associated with a hypersensitive palpable nodule in a taut band. The spot is painful on compression and can give rise to characteristic referred pain, referred tenderness, motor dysfunction, and autonomic phenomena.[81]

Myofascial trigger points can be classified as active or latent. Active trigger points will cause/duplicate the patient's pain when stimulated by compression. A latent trigger point rarely causes pain unless stimulated. When a trigger point is stimulated, the referral pain can have a different degree of severity and quality. It can vary from mild, moderate to severe pain, usually with a deep dull ache quality. Pain can also be exacerbating by jaw function. It is important to recognize that the pain originating from myofascial pain does not follow segmental or neurologic patterns, but it may occur in the same dermatome, myotome, or sclerotome. However, this is not always observed.[82]

All masticatory and cervical muscles can suffer from myofascial pain. The most common muscle groups affected in the orofacial region are the masseter and temporalis muscles. These are the biggest masticatory muscle groups, and also, the cervical muscles are commonly involved, such as the trapezius, splenius capitus, and sternocleidomastoid.

Trigger points in the superficial masseter muscles can refer pain to the eyebrow, maxilla, mandible, mandibular, and maxillary posterior teeth. The deep layer of the masseter muscles can refer pain to the ear (Fig. 40.7). Trigger points in the temporal muscles can refer pain to the posterior maxillary teeth temporal region frontal area above the eyebrow.



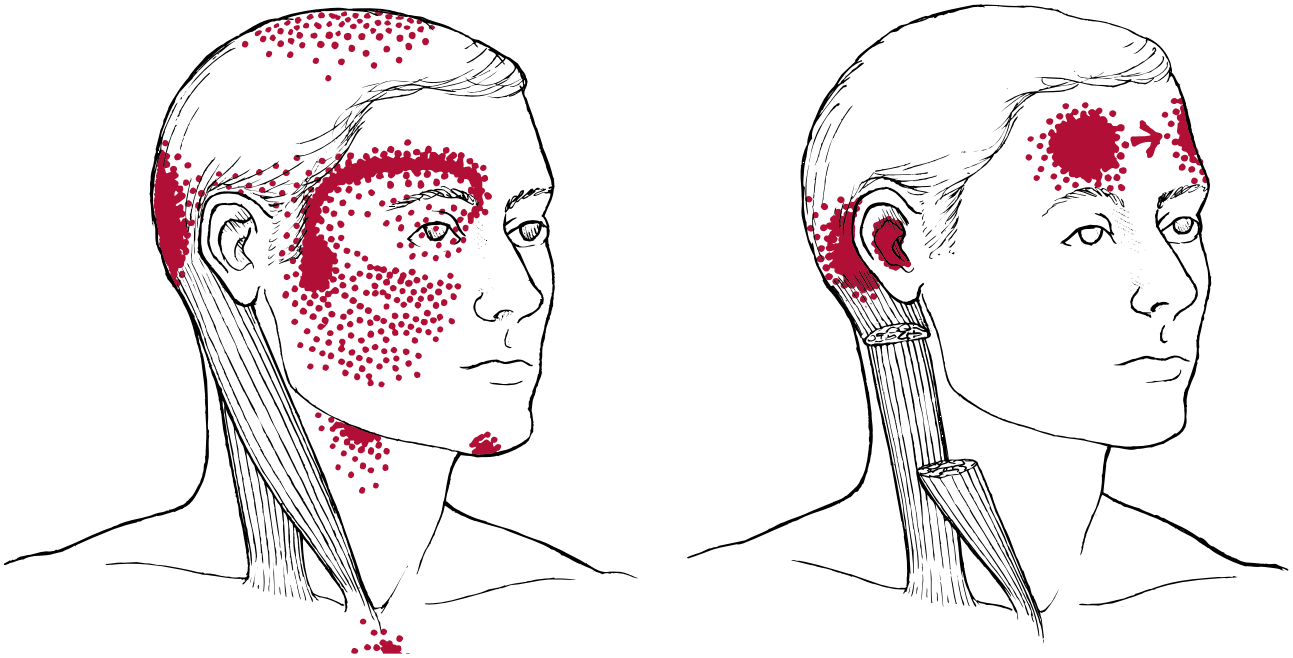
• **Figure 40.8** Referred pain pattern from trigger points located in the most vertical fibers of the upper portion of the trapezius muscle. Solid red shows the essential referred pain zone whereas the stippling maps the spillover zone. (From Donnelly JM: Travell, Simons and Simons' Myofascial Pain and Dysfunction. Third edition. Baltimore, MA: Williams & Wilkins, 2018.)

Cervical muscles trigger points can also refer pain to the head and face and duplicate headaches and facial pain (Figs. 40.8 and 40.9).

According to DC/TMD,[17] myofascial pain is defined as pain of muscle origin as described for myalgia with pain increasing beyond the site of palpation but within the boundary of the muscle when using the myofascial examination protocol.[76]

Positive for both:
1. pain in the jaw, the temple in the ear, or in front of ear AND
2. pain modified with jaw movement, function, or parafunction

Positive for:
1. confirmation of pain locations in the temporalis or masseter muscles AND
2. report familiar pain with palpation of the temporalis and masseter muscles AND
3. report pain spreading beyond the site of palpation but within the boundary of the muscle



• **Figure 40.9** Note how trigger points located in the sternocleidomastoideus refer pain to the temple area typical temporal headache. Note how trigger points located in the trapezius muscle (marked as a star) refer pain to behind the ear, the temple, and the angle of the jaw. (From Donnelly JM: Travell, Simons and Simons' Myofascial Pain and Dysfunction. Third edition. Baltimore, MA: Williams & Wilkins, 2018.)

For myofascial pain with referral, the pain is will refer beyond the boundary of the muscle being palpated when using the myofascial examination protocol. Spreading pain may also be present if positive for both:

1. pain in the jaw, temples ear or in front of ear; AND
2. pain modified with jaw movement, function, or parafunction

And positive for:

1. confirmation of pain locations in the temporalis or masseter muscles AND
2. report familiar pain with palpation of the temporalis and masseter muscles AND
3. report of pain at the site beyond the boundary of the muscles being palpated

Disturbances of motor functions caused by trigger points include spasms of other muscles, weakness, loss of coordination, and decreased work tolerance of the involved muscle. The weakness and loss of work tolerance are often interpreted as an indication for increased exercise. However, if this is attempted without inactivating the responsible trigger points, the exercise is likely to encourage and further ingrain substitution by other muscles with further weakening and deconditioning of the involved muscle.

Management for Temporomandibular Disorders

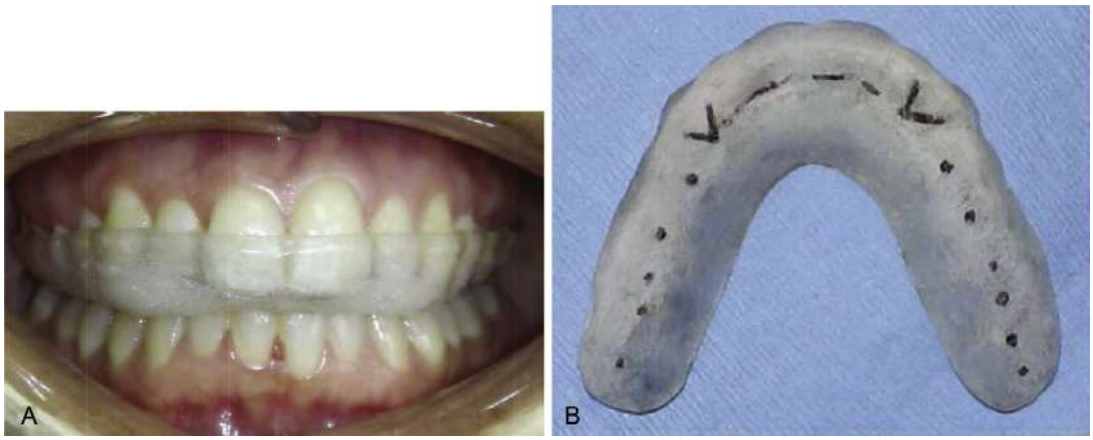
The overall management goals for TMD mimic those of other orthopedic or rheumatologic disorders. Since the etiology of TMD is multifactorial, a multi-disciplinary approach should be used to encompass several treatment modalities that address specific etiologic factors and comorbidities associated with it.

Based on an international consensus, the first line approach for the management of TMD should be evidence-based, reversible, and conservative (non-invasive).[83,84]

Management of TMDs consists of a combination of self-care, cognitive behavior therapy, physical therapy, pharmacotherapy, oral appliance therapy, physical medicine, and alternative medicine such as acupuncture and medical massage therapy, and surgery. Surgery is performed only to treat structural anatomic pathology that is producing pain and dysfunction and after at least six months of a trial of failed conservative treatment. Surgical procedures include arthrocentesis, arthroscopy, open arthrotomy, and combined joint and reconstructive jaw procedures.

Self-care modalities are helpful to allow patients to know their oral habits, posture, and other factors that contribute to the perpetuation of their problems. Once patients know oral parafunction habits, it is easier to control or eliminate them. Application of thermal therapy with ice or heat, 15 to 20 min several times a day, can also be beneficial. Avoiding hard and chewy foods and maintaining a soft food diet can help reduce the stress and pressure into the masticatory muscles and TMJ. Recognizing and eliminating oral habits such as clenching teeth, gum chewing, biting nails, lips, cheeks, and objects such as pens/pencils and others can also reduce stress into the masticatory system.

Oral appliances have been the treatment of choice for many TMD for decades. Several names were designated to it, such as oral orthotics, mouthpieces, occlusal appliances, and others. Several models/designs have been developed over the years with the aim to provide a better maxilla-mandibular relationship, more stable TMJ position, and better and stable occlusion. An extensive review of the literature demonstrated that the effectiveness



• **Figure 40.10** A, Stabilization appliance B, Occlusal contacts have been marked. Note that in the musculoskeletal stable position of the condyles (centric relation), there are even and simultaneous contacts of all posterior teeth (cusp tips contacting flat surfaces). Eccentric guidance is provided by the canines. With permission from Dr. Okeson.

of oral appliances is between 70% and 90%,[85] and that, in general, they help to reduce TMD symptoms.[86–88] Despite this, the evidence for their effectiveness in the management of TMD is poor to moderate.[89–92] However, dentists worldwide still use it to some degree of success. In general, for the management of TMD, a hard-acrylic stabilization appliance with anterior guidance is recommended for both myogenous and articular pain, and in cases of TMJ disc displacement, an anterior repositioning appliance could be used to help reduce the load and promote healing of the retrodiscal tissues (Fig. 40.10).

Physical therapy modalities including manual therapy, dry needling, iontophoresis, ultrasound, TENS, and low level laser therapy can help to improve muscle pain conditions and TMJ pain. The general concept is that physical therapy modalities will help reduce pain and improve the function of the masticatory and cervical muscles and TMJs. The evidence varies according to the study, and some conclusions recommended further and longitudinal investigations.[93–104]

Cognitive behavior therapies aim to reduce patients' maladaptive behaviors and increase adaptive cognitions and behaviors.[105] Several studies[105–108] demonstrated that this management modality is helpful for patients suffering from TMD and also for patients with TMD and other comorbidities.

Pharmacotherapy is a well known treatment modality for TMD. Several classes of medication are known to help with the management of TMD, from acuter to chronic TMD these medications include nonsteroidal anti-inflammatory drugs, muscles relaxants, corticosteroids, anti-depressants, anti-anxiety medications, and anti-convulsants.[109–111]

Oral surgical procedures are also indicated in the management of TMD. Most often, these procedures are not indicated prior to a trial and failure of non-invasive conservative treatment unless a more severe condition such as TMJ tumor, growth disorders, or severe OA of the TMJ where the dental occlusion is affected or misaligned of the jaw occurred and cannot be correct by conservative treatment.[112–115]

Botulinum toxin type A has been used to manage TMD and other facial pain conditions for many years, especially for masticatory muscles disorders, migraines, and bruxism, despite its clinical efficacy. The evidence of botulinum toxin type A in the management of TMD is still lacking.[116–121] Platelet rich plasma and hyaluronic acid have been used for the management of TMD for many years. Recent evidence suggests that these management modalities may be beneficial for TMD and myofascial pai. However, more studies need to be performed to verify their long term efficacy.[122–125]

Neurovascular Pains: Orofacial Manifestations of Primary Headache Disorders

The International Classification of Headache Disorders (ICHD-3) describes headaches as pain located in the head, above the orbitomeatal line and/or nuchal ridge. The first part of the ICHD-3 is dedicated to the classification of the primary headaches, including migraine and trigeminal autonomic cephalalgias (TAC). Facial pain occurring below the orbitomeatal line, anterior to the pinnae, and above the neck is not an integral part of the classification of the primary headaches in the ICHD-3. The classification only acknowledges that otherwise typical patients suffering from migraines without aura could have pain located in their face, "facial migraine."[20]

However, there are several reports in the literature describing patients with orofacial pain that resemble primary headaches. The most compelling evidence is for the migraines without aura (Mw/oA) and the TAC, especially cluster headaches (CH).[126–138] The evidence for orofacial pain resembling other primary headaches, the fourth group of the primary headaches in the ICHD-3, and tension type headaches (TTH) is scarce.[20,139] Recently, a case series presented four patients with paroxysmal facial pain that resemble primary stabbing headaches.[101] Regarding TTH, the overlap between the characteristics of TTH and masticatory myofascial pain may prevent the differentiation between these two entities.[140]

When pain is felt in the orofacial region, dentists are likely the first healthcare provider to see patients seeking resolution.[20] In a survey of Dutch general practitioners, neurologists, and patients that aimed to describe the clinical features that could account for the diagnostic delay of CH, they established that 34% of patients had a consultation with a dentist and 33% saw an ear nose and throat (ENT) specialist before diagnosis, that presence of typical migraine symptoms (nausea, vomiting, and photophobia), and lower age at onset delayed the correct classification.[137] In a sample of 230 patients diagnosed with CH, dentists and ENT surgeons were the healthcare professionals most commonly consulted

before a referral to a neurologist; 45% of patients saw a dentist and 27% an ENT.[141]

Facial pain is commonly associated with intraoral structures like teeth, periodontal and oral mucosa, masticatory muscles, and TMJ. However, primary headaches (neurovascular pain), painful posttraumatic trigeminal neuropathy can mimic a toothache.[142] Dentists are well trained to recognize pain from dental origin. However, unexplained pain in the orofacial region should also raise the possible diagnosis of an atypical presentation of primary headaches or neurovascular orofacial pain.[126,127,134,138,143–145] Failure to recognize orofacial pain resembling primary headaches increases the time of a correct diagnosis, inflicts unnecessary, irreversible treatments, like root canals and extractions, and prolongs patient suffering.[128,140,146–148] Therefore early detection of these disorders is imperative.[141,143]

Until recently, there was no comprehensive, internationally acceptable comprehensive classification for orofacial pain, making it difficult to study the incidence/prevalence, pathophysiology, and treatments of several orofacial pain conditions, including facial pain resembling primary headaches.[19,143] In 2020, the International Classification of Orofacial Pain, first edition (ICOP), was published to fill out this gap. To the interest of this chapter, the ICOP has a dedicated section to primary neurovascular orofacial pains that resemble the presentations of primary headaches in patients with de novo pain in the facial area reminiscent of primary headaches.[18] Table 40.1 summarizes the primary headaches and their orofacial pains counterparts according to the ICHD-3 and ICOP, respectively.

TABLE 40.1 Primary Headaches and OFP Resembling Presentations of Primary Headaches

Primary Headache Pain ICHD-3[1]	Orofacial Pain Counterpart ICOP	Possible Differential Diagnosis[4]
Migraine	Orofacial migraine	NVOP
TTH	Tension type OFP	Myofascial OFP
TACs		
Cluster headache	Orofacial cluster headache	Tolosa-Hunt syndrome Maxillary sinusitis
Paroxysmal hemicrania	Paroxysmal hemifacial pain	
SUNCT/SUNA	SUNFA	
Hemicrania continua	Hemifacial continuous pain with autonomic symptoms	Temporal arteritis Raeder paratrigeminal neuralgia Trigeminal neuralgia Pulpitis
Not applicable	NVOP	Painful posttraumatic trigeminal neuropathy
ICHD-3	International Classification of Headache Disorders, third edition	
ICOP	International Classification of Orofacial Pain, first edition	
TTH	Tension type headache	
NVOP	Neurovascular orofacial pain	
OFP	Orofacial pain	
TMD	Temporomandibular Disorders	
TACs	Trigeminal Autonomic Cephalalgias	
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing	
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)	
SUNFA	Short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic symptoms	

Pathophysiology

Orofacial manifestations of primary headache disorders most likely share the pathophysiology of their headache counterparts. However, the recent ICOP classification will facilitate studies to investigate the pathophysiology of these conditions.[18,144] The pathophysiology of migraine is discussed elsewhere in this book; the pathophysiology of the TACs is briefly presented below.

Cluster headache is the TAC with more information regarding its pathophysiology. The trigeminovascular system, the parasympathetic nerve fibers (trigeminal autonomic reflex), and the hypothalamus are interacting during CH pain attacks.[149] The trigeminal autonomic reflex has its afferent fibers from the ophthalmic division of the trigeminal nerve and efferent pathway from cell bodies in the superior salivatory nucleus, whose outflow through the seventh cranial nerve synapses in the sphenopalatine ganglion and then projects through the greater superficial petrosal nerve.[150] The region of the posterior hypothalamic area seems crucial in the expression of the disorder since it is seen to be activated on imaging studies, and because of CH circadian periodicity, with attacks frequently occurring at night and following a seasonal pattern.[149–152] Extremely important is to rule out pathology of the pituitary gland in the etiology of TAC, since pituitary and peripituitary gland pathology may present as a phenotypic TAC, because of that, it is recommended that a brain MRI scan with pituitary views and pituitary function tests be done as part of workup in all TAC.[150,153,154]

Orofacial Migraine

Orofacial migraine (OM), also referred to as lower-half migraine or facial migraine, is the only primary headache that the ICHD-3 acknowledges could be located in the facial area.[20] The ICOP refers to this migraine as OMs.[18]

According to the ICOP, OM is facial and/or oral pain with characteristics and associated features of migraine without aura according to the ICHD-3.[18,20] OM lasts from 4 to 72 h when it is not treated, or it is unsuccessfully treated, its pain has at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe, aggravation by routine physical activity. In addition, OM has one or both associated features: nausea and/or vomiting, photophobia, and phonophobia.[18] Orofacial migraine can be episodic or chronic. Patients suffering from episodic OM

have at least five attacks. Like migraines, chronic OM has to be present for more than three months, with orofacial pain occurring for 15 or more days per month, and at least eight days have migraine features.[18,20,155]

The ICOP reserves this diagnosis for headache naïve patients with exclusively facial and/or oral pain. Orofacial migraines are rare, and if facial and/or oral pain that meets the criteria for OM is accompanied by headache, the ICHD-3 should be used for its classification.[18]

Epidemiology

Several studies report the presence of migraine with orofacial pain involvement. There are numerous cases reported in the literature. Overall, data show that migraine with head pain and orofacial pain is uncommon and that OM, pain with migraine characteristics only in the facial region, is extremely rare.[126,131–133,135,136,138,146,156–159]

An epidemiologic study of the German Headache Consortium, where 3,351 participants responded to a survey sent to 6,000 people, showed a prevalence of migraine equal to 15.4%, 517 individuals. Almost 30% of the individuals suffering from migraines reported recurrent facial pain. One participant, a 42-year-old male, had migraine pain located only in his lower face. However, he had a previous history of typical migraines. Of the individuals suffering from migraines and facial pain, 80% were women. Patients with migraine and facial pain reported more autonomic symptoms (conjunctival injection, tearing, miosis, ptosis, eyelid edema, nasal congestion, facial flush) than patients with head migraine only, 47% and 7.5%, respectively ($P < 0.001$).[159]

In a tertiary headache and facial pain outpatient clinic, the prevalence of independent facial pain, or facial pain associated with headaches was assessed in 2,912 patients. Patients were divided into three groups: patients that the headache was accompanied by concomitantly face pain (type I), patients that headache pain ceased, followed by facial pain with the same characteristics of the original headache pain (type II), and the last type, patients that have never suffered from headaches attacks and developed de novo orofacial pain (OFP) with similar characteristics of primary headaches (type III).[138] In this group, where 1,935 patients had a migraine or probable migraine, 44 patients (2.3%) had migraine with facial involvement. Looking at these 44 patients, 90% of patients were females. The patient's average age and migraine mean age of onset were 43.2 (SD 14.4) and 30.5 (SD 15.8) years old, respectively. Thirty-eight patients (1.9%) were type I patients, five (0.25%) were type II patients, and only one (0.05%) patient had OM as classified by the ICOP.[18,138] The mandibular branch of the trigeminal nerve was only involved in four patients, and aura symptoms was present in type I patients where the pain was mainly felt in the ophthalmic branch of the trigeminal nerve.[138]

In a prospective audit in a multi-disciplinary facial pain service in England, from 3900 patients assessed, 1176 (30%) had a migraine, including 58 patients with migraine presenting as isolated facial pain (1.4%). The 58 patients included patients that were not naïve to migraine with head pain. However, at the time of assessment, their pain was exclusively in the maxillary (V2) and mandibular (V3) trigeminal nerve branches. Facial pain was mostly present in the V2 branch of the trigeminal nerve, while only 12 (5%) had pain in the V3 branch. Almost 80% of the patients were females. Twenty-three of these patients reported rhinorrhea or nasal blockage, 12 reported lacrimation, eight reported conjunctival injection, two ptoses, eight miosis, and two patients reported facial redness.[158]

Treatment

At this time, there are no published clinical trials investigating a specific drug or intervention for the treatment of OM. However, the literature suggests that OM is responsive to migraine treatments. For example, Gaul et al. reported two cases that responded to migraine specific medications: a case of a 44-year-old healthy female with probable OM that was successfully treated with zolmitriptan 2.5 mg, and another case of a patient with migraine pain located mostly in the maxillary front teeth that responded to combination drug containing ergotamine and diclofenac.[133] A study in a rhinologic setting, 51 patients with migraine pain in the head and face pain did not respond to medical or surgical treatment for rhinosinusitis. However, these patients benefited from antimigrainous medication (sumatriptan, pizotifen, amitriptyline, propranolol, ergotamine, and aspirin), 24 of these patients had pain isolated to the maxillary branch of the trigeminal nerve.[131] In a prospective clinical audit, 58 patients with migraine pain isolated to the maxillary and mandibular branches of the trigeminal nerve, 23 of 30 patients taking triptans successfully and consistently had resolution of facial pain episodes with triptans, and 16 of 40 patients had a reduction in pain episodes after discontinuation of daily intake painkillers. This audit also noted that patients reported that preventive medications were beneficial. The preventive treatments and number of patients using were tricyclic anti-depressants (nine patients), propranolol (four patients), candesartan (nine patients), topiramate (four patients), gabapentin (three patients), pregabalin (one patient), and botulinum toxin type A (four patients). Four patients reported benefit from greater occipital nerve blocks. [158]

Dental treatments like root canals, extractions, dental restoration, TMJ surgery, and other treatments like sinus surgery are ineffective and should be avoided at all costs.[131,158]

More research is needed regarding the treatment of OM and migraines where the main location of the pain in the orofacial structures. For example, we do not know if anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies or small molecules CGRP receptor antagonists are viable treatments for OM.

Tension Type Orofacial Pain

According to the ICOP, tension type orofacial pain (TTOP), episodic or chronic, is pain in the orofacial region, without head pain, with characteristics associated with tension type headache.[18,20] However, the ICOP does not provide a diagnose criteria for TTOP because of insufficient evidence to differentiate among TTOP, TTH, and myofascial orofacial pain.[17,18,20]

Trigeminal Autonomic Orofacial Pain

The ICOP defines trigeminal autonomic orofacial pain as pain attacks with characteristics and associated features of the TAC that occur exclusively in the orofacial region without head pain. Suppose orofacial pain is associated with head pain in this case the TAC should be classified according to the ICHD-3.[18,20] TAC, a group of primary headaches, are severe, unilateral headaches with prominent cranial parasympathetic autonomic features ipsilateral to the pain. TAC are differentiated according to attack duration, frequency, and response to treatment.[20] Like the ICHD-3, the ICOP has four subtypes of trigeminal autonomic orofacial pain: orofacial cluster attacks, paroxysmal hemifacial pain, short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic

symptoms (SUNFA), and hemifacial continuous pain with autonomic symptoms.[18,20]

Orofacial Cluster Attacks

Stereotypical CH attacks are severe, strictly unilateral, located in the orbital, supraorbital, and temporal region, lasting 15 to 80 min and occurring once every other day and eight times a day. Further, the pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema. Patients can also present a sense of restlessness and agitation. The circadian periodicity, active and inactive periods, is a primary feature of CH.[150] CH can be episodic or chronic. In episodic CH, attacks occur in periods lasting from seven days to one year, separated by at least three months without pain. In chronic CH, headache attacks occur for one year or longer without remission or with a remission period of less than three months.[20] Orofacial cluster attacks (OCA) have the same characteristics. However, occurring unilaterally in the face and oral region. Several case reports in the literature describe CH in the maxillary and mandibular branches of the trigeminal nerve.[129,132] Some of these reports mentioned pain in the orofacial region only, while a toothache is the chief complaint for others.[91,94,156] Patients often consult with dentists for pain resolution since the pain of CH and OCA is very similar to dental pulpitis, which can lead to diagnosis delay and unnecessary treatment.[127,140,141,144,145]

Paroxysmal Hemifacial Pain

Paroxysmal hemicrania (PH), as described by the ICHD-3, are attacks of severe, strictly unilateral pain in the orbital, supraorbital, temporal regions. The attacks last 2 to 30 minutes and occur several or many times a day. The attacks are usually associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema. Patients can also present a sense of restlessness and agitation.[20,150] Like CH, PH can be episodic or chronic. In episodic PH, attacks occur in periods lasting from seven days to one year, separated by at least three months without pain. In chronic PH, headache attacks occur for one year or longer without remission or with a remission period of less than three months.[20] Importantly, they have an absolute response to indomethacin.[20] Paroxysmal hemifacial pain (PHP) has the same description as PH, however, with strictly hemifacial pain attacks.[18] The literature also describes cases of PH presenting as a toothache, and like CH, there are reports of unwarranted dental treatment for PH.[128,146,156,160]

Short-Lasting Unilateral Neuralgiform Facial Pain Attacks With Cranial Autonomic Symptoms (SUNFA)

Short-lasting unilateral neuralgiform headache are described as moderate or severe, strictly unilateral, pain attacks occurring in any trigeminal distribution. Pain attacks last 1-600 s, occurring at least once a day, and are usually associated with prominent lacrimation and redness of the ipsilateral eye.[20] Attacks can take three known patterns: short-lived single stabs, groups of stabs separated by short periods of no pain, and longer attacks with many stabs in which the pain does not return to baseline (saw-tooth pain pattern).[20,150] SUNFA has the same description above but without head pain. Both of these entities can be further divided between episodic and chronic. Similar to the CH and PH, chronic diagnosis is given when there is no remission between pain attacks for at least one year, or remission period is less than three months.[18,20,150]

Hemifacial Continuous Pain With Autonomic Symptoms

Hemicrania continua is a persistent, strictly unilateral headache that varies in intensity with associated autonomic signs (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead, and facial sweating, miosis, ptosis, and/or eyelid edema) and/or with restlessness or agitation. The headache is sensitive to indomethacin.[20,150] Migraine symptoms like nausea, photophobia, and phonophobia are more likely to be present during periods of exacerbations.[112] There are reports of pain referral to oral and facial structures, which can complicate the diagnosis.[156,161]

Trigeminal Autonomic Orofacial Pain: Epidemiology

Among the TAC, CH is the most studied condition, and its prevalence is below 0.1%. According to pooled data from studies dated between 1978 and 2009, the one year prevalence is 124 per 100,000 persons (95% confidence interval 101–151), and its lifetime prevalence is 53 per 100,000 persons (95% confidence interval 26–95).[162,163] Cluster headache is more prevalent in males. However, the ratio between males and females has changed over time, 6.2:1 in the 1960s to 2.1:1 in the 1990s. In a meta-analysis of population studies, the overall male to female ratio was 4.3:1.[163] The one year incidence of CH ranges from 2 to 10 per 100,000.[162] In an Italian study, the average age of CH onset was 30.4 years.[164] The suggested mean age of onset between studies varies from 26 to 30 years.[162] Episodic CH is more common than a chronic manifestation of this headache.[150] There are no population studies reporting the incidence and prevalence of OCA. In a study of 608 patients suffering from CH, 330 (54%) had lower syndrome where pain involved at least one infraorbital region. However, it might also extend to the orbital branch of the trigeminal nerve.[129]

PH is a rarer condition than CH. Its prevalence is calculated to be 1% to 3% of CH.[146,165,166] PH onset is between 20 and 40 years, with a mean age of 34 years.[146,166,167] It has the same ratio between males and females, or, it is more prevalent in females with a male to female ratio of 1:2.[129] There are no population studies reporting the incidence and prevalence of PHP.

Similar to the PH, there are no population epidemiologic studies that report the incidence and prevalence of hemicrania continua. However, its prevalence may be higher than expected.[148,166] In a review article, the mean age of onset was 34 years, and the female to male ratio was 1.8:1.[167] However, when summarizing all cases for which gender data are available, a ratio of 2.4:1 can be expected.[166]

The prevalence and incidence of the short-lasting unilateral neuralgiform headache, and its orofacial counterpart, short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic symptoms (SUNFA), are unknown.[165]

Trigeminal Autonomic Orofacial Pain: Treatment

Treatment for CH can be abortive when treatment is targeted to abort cluster attack or prophylactic when medications are used to reduce numbers of attacks.[149,150] There is good evidence that cluster headache attacks are responsive to subcutaneous

sumatriptan within 15 minutes of a single dose, sumatriptan, and zolmitriptan nasal sprays. Cluster attacks also respond to inhalation of 100% oxygen through a high-flow mask at a flow rate of 12–15 L/min.[149,150,168] Lidocaine dripped or sprayed into the ipsilateral nostril is an alternative for patients that triptans are contraindicated or do not respond to oxygen.[111]

Verapamil is considered a first line preventive treatment for long cluster periods or chronic CH. A limited course of corticosteroids can be useful until an optimal dose of other preventives is achieved.[112] High doses of verapamil may be required to be effective, up to 960 mg. Recognizable side effects are gingival hyperplasia, constipation, leg swelling, and cardiac dysrhythmias. Because of the effect of verapamil on heart function, electrocardiogram (ECG) monitoring is necessary. An ECG should be done before and after each increase in dosage and every six months after the dose is established.[111,112] Lithium and topiramate are also used to prevent CH.[111,112] There is evidence that Galcanezumab, a CGRP, humanized monoclonal antibody, reduces the weekly frequency of CH attacks across weeks one to three compared with placebo. However, during weeks four to eight, there was a convergence of results between these treatment groups.[169,170] Electrical stimulation of peripheral structures, like sphenopalatine ganglion, occipital, and vagus nerve, are effective in reducing pain attacks frequency.[111,171–173]

PH, hemicrania continua, and their orofacial counterparts are responsive to indomethacin.[112,167] However, when the treatment with indomethacin is not feasible, cyclooxygenase two selective inhibitors, topiramate, greater occipital nerve block with lidocaine, and methylprednisolone can be effective for some patients.[19,174–176]

Regarding the management of the short-lasting unilateral neuralgiform headache, lamotrigine is the most effective drug; gabapentin, topiramate, and lidocaine IV infusion may also be effective.[150]

Neurovascular Orofacial Pain

The ICOP defines neurovascular orofacial pain (NVOP) as moderate to severe pain in the intraoral region without head pain, although pain referral to adjacent regions is possible. NVOP presents with toothache-like symptoms, or it is pulsating, with at least one mild autonomic and/or migraine symptom. Pain attacks can be relatively short (1–4 h) or long, lasting more than 4 h.[30] Case reports suggest the evidence of dental hypersensitivity to cold without any dental pathology, which can lead to delay in diagnosis and wrong treatment.[134,144,155,177,178] Hypersensitivity to cold, the later mean age of onset, and a higher ratio between females and males (3:1) differentiates this condition from OM.[179] Importantly, as mentioned in the ICOP, NVOP needs a thorough and prospective examination.[18]

Epidemiology

The prevalence of NVOP pain varies from 7% to 52%, depending on the study population.[126,180,181] NVOP was first described in 1997.[126] In this prospective study, 29 (52%) patients, among 55 patients with neurovascular facial pain, could not be classified as suffering from migraine without aura, cluster headache, or PH. The intraoral pain of these 29 patients was severe and episodic, lasting minutes to hours, 42% of patients reported pulsatile pain, and 55% reported at least one autonomic or migraine symptom, nausea being the most common, followed by photophobia and phonophobia. In this group of patients, the mean age of pain onset was 42.6 years old (range 17 to 66 years old), and 70% were female.[126] A different study diagnosed 23 (7%) patients with NVOP among 328 patients from an orofacial pain clinic. In this group, the mean age of onset was higher than in migraineurs, 39.4 (SD ± 13.6) years old, and more common in women.[182] In a cohort of 170 patients suffering from painful posttraumatic trigeminal neuropathy (PTTN) and NVOP, 90 patients had NVOP (52%), and there were no differences regarding mean patient's age, pain onset, and pain intensity.[134] To understand better the incidence and prevalence of NVOP, more sophisticated epidemiologic studies are necessary.

Treatment

Similar to the other orofacial manifestation of primary headaches, NVOP does not answer to dental treatments.[126,142,179,180] NVOP responds to classical preventive and abortive anti-migraine drugs like triptans and propranolol.[126,178,180] However, NVOP response rate to triptans may be lower than in typical migraines. Also, chronic cases with comorbid muscle pain have good results with amitriptyline.[182]

Neuropathic Orofacial Pain

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory system.[183] The prevalence of chronic neuropathic pain in the general population is estimated to be 7% to 10%.[184,185] The prevalence of neuropathic pain following surgical interventions in the oral cavity is low, or underdiagnosed, considering the number of procedures done by dentists, or, possibility because of the ubiquitous use of local analgesia.[186]

Neuropathic pain can be classified according to its location, etiology, syndromology (neuralgia or neuropathy), and duration. However, a widely accepted classification for neuropathic pain does not exist.[20,22] Central neuropathic pain is caused by a lesion or disease of the central nervous system (spinal cord and/or brain), for example neurodegenerative or cerebrovascular diseases. Conversely, peripheral neuropathic pain pathology involves small nerve fibers (C fibers, Aβ, and Aδ fibers).[187] Paroxysmal neuralgias are episodic neuropathic pain characterized by sudden bursts of electric-like pain that project heterotopically along nerve distribution. In contrast, continuous neuropathic pains are continuous, unremitting pain with varied intensity.[22]

Pathophysiology of neuralgias and neuropathy pain can be found somewhere else in this book. Below we discuss the most relevant neuropathic pain in the orofacial region according to the ICHD-3.[20]

Cranial Neuralgias

Neuralgias can rise from cervical and craniofacial nerves, for example, the trigeminal nerve, nervus intermedius, glossopharyngeal, vagus, and occipital nerves. There are common characteristics among the neuralgias: paroxysmal, brief, and intense pains described as sharp, lancinating, stabbing, or lightning-like within the distribution of a particular nerve. They are often associated with triggers (e.g. brushing teeth, shaving), and presence of a refractory period.[188] Sodium channel blockers are usually the first line treatment for neuralgias.[188] Cranial neuralgias may or may not have a secondary cause. However, evidence of sensory changes imposes evaluations (neurophysiologic, radiographic, and laboratory evaluation) to identify secondary etiologies.[189] Highlighting

the importance of this is the "numb-chin" sign of trigeminal branch mental neuropathy, which is associated with high mortality because of its frequent association with malignancy.[188,189]

Trigeminal neuralgia (TN) is one of the most studied cranial neuralgia and is discussed in detail below.

Glossopharyngeal neuralgia is less common than TN, and both entities may exist in the same patient.[188] It is described as unilateral brief stabbing pain, abrupt in onset and termination, in the distributions not only of the glossopharyngeal nerve but also of the auricular and pharyngeal branches of the vagus nerve. Pain is experienced in the ear, base of the tongue, tonsillar fossa, and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking, or coughing and may remit and relapse in the fashion of TN.[20]

Occipital neuralgia is described as unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the greater, lesser, and/or third occipital nerves, sometimes accompanied by diminished sensation or dysesthesia in the affected area, and commonly associated with tenderness over the involved nerve(s).[20] Patients suffering from occipital neuralgia may benefit from nerve blocks with local anesthetic and corticosteroids, neuropathic pain medication, and physical therapy. More invasive treatments, such as pulsed radiofrequency ablation, occipital nerve stimulation, or a trial of botulinum toxin, may be considered if conservative treatment fails.[188]

Trigeminal Neuralgia

TN is characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli. It may develop without apparent cause or result from another diagnosed disorder. Additionally, there could be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s). See Box 40.1 for diagnosis criteria.[20] TN is a clinical diagnosis, based on the stereotypical disorder characteristics: short paroxysmal attacks, severe pain intensity, presence of a trigger zone, refractory period. TN is more prevalent during middle and old age, with the peak age between 50 and 69 years old, its incidence increases with age, and women are more affected than men.[190]

• BOX 40.1 Trigeminal Neuralgia ICHD-3 Diagnostic Criteria[1]

A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,[1] and fulfilling criteria B and C
B. Pain has all of the following characteristics:
   1. lasting from a fraction of a second to 2 min[2]
   2. severe intensity[3]
   3. electric shock-like, shooting, stabbing, or sharp in quality
C. Precipitated by innocuous stimuli within the affected trigeminal distribution[4]
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:
1. In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes.
2. Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for >2 min.
3. Pain may become more severe over time.
4. Some attacks may be or appear to be spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomic location of the trigger, and/or other factors.

Trigeminal neuralgia can be classified into three subforms: classical, secondary, and idiopathic trigeminal neuralgias.[20] Classical TN occurs when the development of the TN has no other apparent cause besides the neurovascular compression.[20,191] When an underlying disease is the cause of the TN, the TN is designated as secondary to the disease. Patients with secondary TN may show sensory changes.[20] Some underlying causes of TN are multiple sclerosis, space-occupying legions, and arteriovenous malformation.[192–194] Idiopathic TN does not have abnormal MRI or electrophysiologic tests.[20] Although TN is a clinical diagnosis, brain imaging investigation (computed tomography or MRI) is critical to rule out secondary TN and possible neurovascular compression.[195]

The ignition hypothesis is the most accepted explanation for the pathophysiology of the TN. According to this hypothesis, TN results from specific abnormalities of trigeminal afferent neurons in the trigeminal root or ganglion.[196]

Treatment

TN is best managed using anti-convulsant drugs. The sodium channel blockers carbamazepine (200–1200 mg/day) and oxcarbazepine (600–1800 mg/day) are considered the first line of treatment.[195] Both drugs need blood monitoring for surveillance of low blood cell counts, liver function, and hyponatremia. Furthermore, genetic testing is warranted for carbamazepine because of the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis.[197,198] There is limited evidence supporting add-on therapy with lamotrigine and baclofen. The efficacy of other drugs used for the treatment of other neuropathic disorders like gabapentin, pregabalin, serotonin-noradrenaline reuptake inhibitors, or tricyclic anti-depressants is unknown.[195]

Surgical treatment is also used in the management of TN. However, there are significant risks associated with these treatments.[199–201] Microvascular decompression is the most effective surgical treatment for patients with classical TN; shorter duration of pain and arterial compression improve outcomes. However, it is associated with meningitis, CSF leak, transient diplopia, wound infections, temporary hearing loss, ataxia, and more permanent hearing loss and death.[201] Balloon compression, glycerol rhizotomy, radiofrequency thermocoagulation, and gamma knife radiosurgery are procedures with a high rate of initial pain relief. However, pain recurrence is more common, and they are associated with facial numbness and dysesthesia, radiation induced neoplasia and vascular injury, cranial palsies, trigeminal motor weakness, and meningitis, among other side effects.[199,200] These procedures could be an alternative for patients that cannot tolerate microvascular decompression.

Painful Trigeminal Neuropathy

The ICHD-3 defines painful trigeminal neuropathy as facial pain in the distribution(s) of one or more trigeminal nerve branches caused by another disorder and indicative of neural damage. It is distinguished from trigeminal neuralgia because the pain is primarily continuous or near-continuous, and commonly described as burning, squeezing, or likened to pins and needles. However,

brief pain paroxysms can occur. There are clinically detectable sensory deficits within the trigeminal distribution, and mechanical allodynia and cold hyperalgesia are common.[18]

Painful trigeminal neuropathy attributed to herpes zoster (pain is present for less than three months) and trigeminal postherpetic neuralgia (pain persists for more than three months) are conditions associated with herpes zoster virus. In both, facial pain is unilateral in one or more trigeminal nerve branches, with variable sensory changes. The ophthalmic branch of the trigeminal nerve is the most affected by the virus. Postherpetic neuralgia is the most frequent chronic complication after herpes zoster, its frequencies increase with age, and herpes zoster vaccination reduces the incidence of both herpes zoster and postherpetic neuralgia.[202] Treatment of these conditions can be topical (capsaicin, lidocaine patches) or systemic with drugs like anti-depressants, and anti-convulsants.[203]

Painful PTTN is unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve, with symptoms or clinical signs of trigeminal pain dysfunction. [134] There is a clear history of a traumatic event (mechanical, chemical, thermal, radioactive) and a positive (e.g. allodynia) or negative (e.g. hypoesthesia) sign of trigeminal nerve dysfunction. The pain is located in the distribution of the trigeminal nerve where trauma occurred and has developed within six months of trauma.[20,186]

Painful trigeminal neuropathy attributed to other disorders is pain developed because of other disorders that are not herpes zoster or trauma. It is a unilateral or bilateral pain in the trigeminal nerve distribution with clinical evidence of positive or negative neurologic signs. This condition could be secondary to multiple sclerosis, space occupying legions, or systemic disease.[20]

Idiopathic painful trigeminal neuropathy is unilateral or bilateral pain in one or more trigeminal nerve branches, indicative of neural damage but of unknown etiology.[20]

The general approach to clinical management in painful trigeminal neuropathy is similar to that for other forms of neuropathic pain and is discussed in Chapter 21.

Persistent Idiopathic Facial Pain and Persistent Idiopathic Dentoalveolar Pain (Previously Atypical Facial Pain and Atypical Odontalgia)

Persistent idiopathic facial pain (PIFP) is defined by the ICDH3 and by the ICOP.[18,20] The ICHD-3 describes PIFP as facial and/or oral pain that is daily recurrent, lasting more than 2 h a day for longer than three months.[20] The ICOP defines PIFP as pain occurring in the facial region, and, for persistent pain occurring intraorally, the ICOP uses the term persistent idiopathic dentoalveolar pain (PDAP).[18]

According to the ICHD-3, in addition to PIFP's daily occurrence, pain is poorly localized and does not follow nerve distribution. PIFP has a nagging, dull, or aching quality. Neurologic examination is unremarkable, and pain from odontogenic origin has been excluded.[20]

The ICOP adds on its notes that PIFP and PDAP pain can be deep or superficial, and may radiate from the mouth to the face or from the face to the mouth. More, it acknowledges that somatosensory changes could be present. The ICOP classification further classifies these conditions according to the presence of somatosensory changes when a quantitative sensory test is available.[18]

In the past, the term atypical facial pain was used for PIFP,[20] and atypical odontalgia and phantom tooth pain were terms used for PDAP.[18,186] Historically, atypical facial pain has been used to describe pain in the trigeminal nerve territory that does not resemble the typical presentation of TN.[185] Although the ICHD-3, the IASP, and the ICOP refer to atypical facial pain as a previously used term for PIFP, the International Statistical Classification of Diseases and Related Health Problems (ICD) has maintained the term atypical facial pain.[2,20] The ICD11 describes atypical facial pain as chronic pain of the face that does not meet other diagnostic criteria: https://icd.who.int/browse11/l-m/en.

Constant Unilateral Facial Pain With Additional Attacks

Constant unilateral facial pain with additional attacks is a mild to moderate intensity, dull unilateral pain with distinct moderate to severe pain attacks that last 10–30 min in the same location. Typical autonomic signs and migraine features are absent in CUPFA.[18]

Burning Mouth Syndrome

Burning mouth syndrome (BMS) is an idiopathic chronic pain condition characterized by intraoral burning or dysesthesia sensation, recurring daily for more than 2 h/day over more than three months in the oral mucosa.[20,204] Dry mouth, alteration in salivary function, and taste disturbances are also present in BMS. However, patients with BMS do not have oral mucosa pathology (white lesion, ulcers, erythema, atrophy, stomatitis).[3] Anxiety and depression are associated with BMS.[204,205] Pain is present for most of the day without any interference with sleep. Some patients report that eating or drinking decreases their pain, but most patients avoid hot, spicy, or acidic food/liquids or alcoholic beverages.[204] The anterior two-thirds of the tongue are the most common site for BMS. However, it can be present at the hard and soft palate, buccal mucosa, floor of the mouth, and lips.[204,206] BMS is more prevalent in middle-aged and older women. The overall prevalence ranges from 0.7% to 7%, increasing to 12% to 18% in post-menopausal women.[206]

BMS is a clinical diagnosis of exclusion after investigations to rule out secondary causes of the syndrome are negative. Health history, physical examination, laboratory tests, possible brain and brain stem imaging, salivary flow rate, and psychometric screening should be part of the patients' workup to rule out conditions such as allergic reactions, infection, galvanism, hypothyroidism, diabetes, menopause, vitamin (B complex, iron, zinc) deficiencies, anemia, gastrointestinal abnormalities, medications adverse effects or drug-drug interactions, Sjögren's syndrome, anxiety, depression, and compulsive disorders.[204,205] Box 40.2 has a list of laboratory tests commonly ordered for the diagnosis of BMS.

Treatment

If a specific etiologic factor causes the BMS, management of the syndrome is guided to the etiology. Management of primary, idiopathic BMS is challenging and can encompass cognitive behavior therapy, topical therapies (1 mg tablet of clonazepam for 3 min and then expectorate, 0.15% benzydamine hydrochloride three times per day, topical capsaicin [0.025% cream], or rinsing with Tabasco sauce and water [1:2-4 solution], salivary substitutes, topical antifungals), and a systemic approach (α-Lipoic acid,

• BOX 40.2 Laboratory Tests Commonly Ordered for the Diagnosis of BMS[2]

Complete blood cell count with differential
Fasting blood glucose
Hemoglobin A1C
Serum iron
Ferritin
Total immunoglobulin E
Vitamin B6, B12, and D
Serum antinuclear antibodies
Anti-Sjögren's syndrome-related antigen A and antigen B (SSA/Ro and SSB/La)
Erythrocyte sedimentation rate
Serum antibodies to *Helicobacter pylori* and oral candida
Viral and bacterial swabs

600 mg per day for two months, clonazepam, 0.5 mg per day at bedtime, serotonin/norepinephrine reuptake inhibitors, pregabalin, gabapentin).[204]

Orofacial Pain and Worrisome Differential Diagnosis

Several pain conditions that can mimic toothache are discussed in this chapter, for example, TMD, TN, migraine, neurovascular orofacial pain. However, there are some pain conditions with sinister outcomes that need to be considered when diagnosing OFP.

Giant cell arteritis (GCA) is an inflammatory disease that affects medium and large arteries, and it is most commonly seen in people over 50 years. Its incidence increases with age. GCA has a predilection for external carotid branches, and a prominent temporal artery is often seen in this disease. Blood vessel biopsy is necessary for definitive diagnosis. Erythrocyte sedimentation rate and C-reactive protein tests are done to aid diagnosis. The classical presentation of GCA is new-onset headache, jaw or tongue claudication, pain or weakness in the masticatory muscles, fatigue, anorexia, and weight loss. Corticosteroid treatment is warranted in this condition. If treatment is delayed, there is a real risk of neuro-ophthalmic complications (blindness, stroke). Loss of vision can occur within hours or days. Therefore treatment should not be delayed.[142,145,207–209]

Cardiac pain commonly radiates to the left arm, shoulder, neck, and face. However, infrequently, it can present as dental pain. Heterotopic cardiac pain needs immediate recognition to aid diagnosis. A thorough history of the pain complaint and examination is warranted, specifically addressing if the is pain precipitated by physical effort.[209,210]

OFP may be provoked by the encroachment of brain tumors, like cerebellopontine angle and middle cranial fossa tumors on pain sensitive structures.[211,212] Also, oropharyngeal carcinoma can present with pain in the posterior mandible. OFP can be present prior to the cancer diagnosis.[213,214]

Conclusion

Pain syndromes that involve the face are very common in clinical practice. Many facial pain syndromes are also unique, given the complex anatomy and specialized sensory innervation of the head, face, and neck. These syndromes represent a clinical diagnostic challenge and deserve special attention. The common descriptive terms for facial pain complaints are frequently misleading. Clinicians should be comfortable distinguishing painful conditions that arise from structural pathology, headache syndromes, oral and facial structures, TMJ disorders, myofascial pain disorders, and primary cranial neuralgias.

Key Points

- Pains that involve the face, head, and neck are very common in clinical practice. These painful conditions are often unique and deserving of special attention.
- The common descriptive terms for orofacial pain symptoms are frequently misleading. To avoid confusion, pain clinicians should be familiar with the International Headache Society's Diagnostic Criteria for Head and Neck Disorders, the ICOP, and the diagnostic criteria for TMD. Clinicians should be comfortable distinguishing painful conditions that arise from structural pathology, neurovascular pain, painful musculoskeletal disorders, and orofacial neuropathic conditions.
- Clinicians should be familiar with the clinically relevant head and neck anatomy features and the distinctive neurobiology of pain transmission in this region.
- Chronic/recurrent painful disorders are extremely common in the head and neck, and myofascial pain disorders are among the most common causes of pain and dysfunction in this group. Myofascial pain overlaps several common diagnoses, including TMJ dysfunction, tension headache, and most occipital neuralgia cases. Clinicians should know the diagnostic features, potential etiologies, and exacerbating factors for such disorders. They should also understand how these factors are associated with the various multi-disciplinary options currently recommended for treatment.
- Clinicians should know the unique anatomy and physiology of the TMJ and how jaw position and dental occlusion can contribute to TMD pain symptoms.
- Oral appliances in conjunction with stress management and physical therapy may be a viable treatment option for patients with TMD.
- TN is a unique neurogenic disorder. Patients who meet the clinical TN diagnostic criteria may benefit substantially from anti-convulsant drugs. When pharmacotherapy is exhausted, surgical treatment could be indicated. Patients with other forms of neurogenic facial pain may have a poorer prognosis.

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Visceral Pain

KLAUS BIELEFELDT

Introduction

Chronic visceral pain is common. Abdominal pain is among the main reasons for physician visits, with more than 12 million consultations each year in the United States.[1] Patients with visceral pain present unique challenges as the pain is often poorly localized, associated with strong autonomic reactions and changes in visceral function. Pain management, in turn, may further alter visceral function, with opioid effects on the gastrointestinal tract providing a good example. These unintended treatment effects on visceral function can exacerbate pain or lead to additional discomfort, thus showing that rational and effective pain management needs to be based on an understanding of the anatomic and physiologic basis of visceral function *and* pain. Lastly, visceral pain may elicit a stronger emotional response in patients than somatic pain, which may lead to increased pain-related disability and affect the transition to chronicity.[2]

Physiologic Basis of Visceral Sensation and Pain

Anatomy and Physiology of Visceral Afferent Pathway

Most viscera arise from midline structures and thus receive bilateral innervation. As a result, visceral stimuli activate both hemispheres of the brain, with a predominance of the left side in most right-handed individuals.[3,4] In addition, organs in the chest cavity and most viscera within the abdomen receive dual afferent innervation with vagal and spinal nerves conveying sensory input to the central nervous system (Fig. 41.1). While vagal fibers do not reach the pelvic organs, the distal colon, bladder, prostate, and uterus also have a complex sensory innervation with afferents projecting through the thoracolumbar (hypogastric) and lumbosacral (pelvic) nerves to the spinal cord.

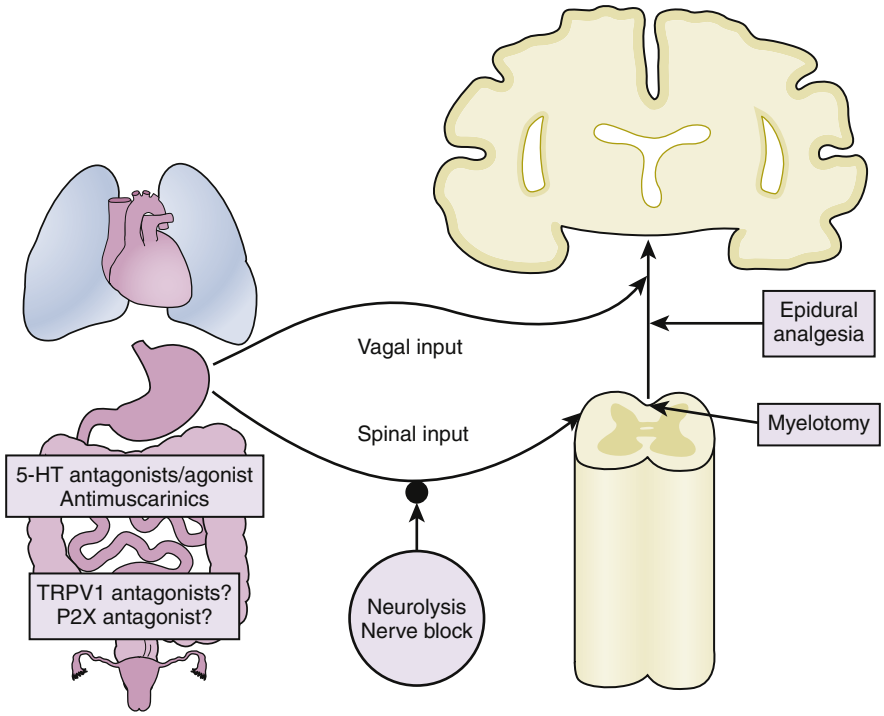
The vagus nerve predominantly comprises afferent fibers (≥80%), which project via the nodose and jugular ganglia to the nucleus of the solitary tract in the brainstem. Spinal afferents pass through the prevertebral (sympathetic) ganglia to the dorsal root ganglia and send their endings to the dorsal horn and central gray of the spinal cord. Information about noxious stimuli is relayed rostrally through the spinothalamic tract. In addition, post-synaptic dorsal horn neurons within the central gray send their central processes through the medial aspect of the dorsal columns, a pathway that has been recognized as uniquely important in visceral pain.[5]

Most physiologic studies characterizing the properties of visceral sensory pathways rely on responses to defined mechanical stimuli. Vagal afferents form a relatively homogeneous group that is activated by low-intensity mechanical stimuli and encodes stimulus intensity over a wide range. The low activation threshold is consistent with the presumed role of these sensory pathways in regulating physiologic processes. In contrast, two classes of mechanosensitive spinal afferents can be distinguished based on their response characteristics: low threshold fibers are similarly activated by low-intensity stimuli and continue to encode stimulus intensity over a wide range, whereas high-threshold fibers are activated by intense, potentially noxious intensities of mechanical stimuli. Thus spinal high-threshold fibers resemble specialized nociceptors that have been described and characterized best in the skin, suggesting that they play a primary role in visceral nociception.[6,7] However, recent studies call such a "specificity" of nociceptive pathways into question as low-and high-threshold fibers project to similar regions in the spinal cord with more intense stimuli recruiting more afferents, a conceptual shift from specificity to intensity coding.[8]

Most studies of visceral afferent pathways rely on mechanical stimulation to identify fibers or neurons projecting to various inner organs. Recent investigations suggest that such a biased search strategy may miss approximately 25% of the primary afferent fibers. While these afferents are referred to as "silent" based on their lack of mechanosensitivity, they likely respond to other stimulus modalities and can be recruited by exposure to inflammatory mediators or chemical signals in the bladder and gut.[9,10] Finally, most visceral sensory neurons are polymodal, meaning they respond to multiple stimulus modalities, including endogenous and exogenous chemicals contained in luminal contents, temperatures (heat or cold), and stretch.

Mucosal Signaling and Visceral Sensation

In the airways, gastrointestinal tract, and urinary bladder, nerve fibers are found close to epithelial cells, which often exhibit specializations with secretory vesicles on the basal surface.[11–13] Structural organization and functional studies suggest that visceral epithelial cells function as an interface between chemical or mechanical stimuli and the nervous system. The best example is serotonin release from enteroendocrine cells in the gastrointestinal tract. The gut is the major source of this signaling molecule and contains 95% of the serotonin in the body. Most of this serotonin is stored in specialized enteroendocrine (enterochromaffin) cells and can be released by chemical or mechanical stimuli, activating intrinsic



• **Figure 41.1** Schematic description of visceral innervation and potential targets for analgesic therapy. As indicated by the arrows, most viscera receive a dual sensory innervation with vagal and spinal afferents. Current symptomatic treatment of peripheral targets relies largely on agents interfering with intestinal contractility. However, the capsaicin receptor (TRPV1) and purinergic P2X receptors constitute promising targets for the treatment of visceral pain. Neurolytic block, myelotomy, and epidural analgesia all target spinal afferent pathways involved in relaying visceral pain.

and extrinsic neurons.[11] Within the urinary tract, epithelial cells release adenosine triphosphate (ATP), which acts on purinergic receptors (P2X receptors) and is involved in normal micturition as well as bladder pain.[14] Bladder epithelial cells also express the capsaicin receptor TRPV1, an ion channel that is activated by acid, temperature, endogenous lipid mediators, and the pungent substance (capsaicin) contained in hot pepper. Animals with a targeted deletion of this channel display altered micturition behavior, again lending to the importance of epithelial cells in visceral sensation.[15] A variety of luminal contents present in the gut can interact with epithelial cells or nerve terminals through the activation of protease-activated-receptors (PAR). For example, PAR-2 receptors are present in the submucosal neurons and extrinsic afferent neurons. Luminal proteases, such as trypsin, protease-released inflammatory cells, or the resident microbiome can cleave the tethered ligand and activate this pathway, thereby contributing to sensitization.[16–18]

Sensitization of Visceral Afferent Pathways

*V*isceral afferents can sensitize in response to inflammation or injury. The release of mediators, such as prostaglandins or bradykinin, rapidly alters the properties of ion channels, leading to an increase in neuronal excitability. In addition, cytokines and growth factors may trigger transcriptional changes, affecting the properties of sensory neurons through alterations in gene expression. As described above, luminal contents may directly affect the functioning of afferent neurons or indirectly influence neuron excitability by activating epithelial or immune cells. Increased peripheral input (*peripheral sensitization*) may secondarily alter sensory processing in the central nervous system (*central sensitization*), with both of these sensitization states contributing to the development and maintenance of visceral pain syndromes. One easily recognized consequence of sensitization of visceral afferent pathways is increased tenderness to palpation over a larger area than what would be expected based on the underlying pathology.[19] Both peripheral and central mechanisms contribute to the increased sensitivity and expanded areas of referred pain, which are common in irritable bowel syndrome (IBS), functional dyspepsia, and patients with painful bladder syndrome (formerly known as interstitial cystitis), or similar disorders.

Central Processing of Visceral Sensation and Pain

Vagal afferents project to the nucleus of the solitary tract and from there via the parabrachial nucleus and ventromedial thalamus to the insular cortex.[20] They form many connections with the hypothalamus, supraoptic nucleus, anterior cingulate cortex, and amygdala, which are essential for autonomic and emotional responses to visceral stimulation.[21,22] Spinal afferents also project to the thalamus. However, they are preferentially found in the posterolateral nucleus, which is connected to cortical areas, including the insula. The lateral components primarily serve discriminative functions associated with pain perception (e.g. location and intensity). At the same time, the medial thalamic nuclei, the main target of vagal input, are more closely linked to emotional and autonomic responses triggered by pain and other visceral inputs. Consistent with the bilateral innervation of organs originating from midline structures, most visceral stimuli activate both cerebral hemispheres, albeit with a preferential activation of one, mostly the left side.[3,23,24] Studies using functional brain imaging have not demonstrated striking differences in the supraspinal processing of visceral and non-visceral pain. However, visceral pain activates the perigenual portion of the anterior cingulate cortex, whereas

non-visceral pain is primarily represented in the mid-cingulate cortex. The physical proximity or even overlap between the processing of visceral pain and emotion in the perigenual portion of the anterior cingulate cortex may well explain the stronger emotional response to painful visceral than non-visceral stimuli.[25–27]

Increased afferent input alters the response properties of second- and higher-order neurons, potentially leading to lasting functional and even structural changes. In addition, factors independent of specific peripheral input, such as anxiety with associated hypervigilance, affect descending modulating mechanisms, which can also facilitate synaptic transmission along afferent pathways and affect the perception and impact of pain. More recently, the potential contribution of glial cells has generated new insights into the role of non-neuronal cells in synaptic plasticity, thereby opening another potential venue for targeted pain management strategies.[28] While experimental approaches typically focus on selecting mechanisms contributing to sensitization, clinicians face the combined impact of synaptic plasticity of afferent pathways driven by different processes, such as inflammation or cancers, compounded by central states or traits, such as anxiety or arousal with anticipation or altered sensory processing and the associated changes in descending modulation. Thus agents affecting a single step or process will have more limited efficacy in clinical practice than in more controlled experimental settings.[29] The mechanisms of central sensitization and potential treatment strategies are not unique to visceral pain and are discussed in more detail in Chapters 8 and 9.

Visceral Pain Stimuli

Visceral events that can produce a conscious sensation or acute pain in humans include traction of the mesentery, distension of hollow organs, strong contractions of muscle layers surrounding such hollow organs, ischemia, and chemical irritants.[19,30] As routine endoscopic interventions have been established, cutting or burning—two clearly noxious stimuli when applied to the skin—are not perceived when applied to the viscera, thus setting visceral apart from non-visceral sensation. Because of its sensitizing influences on sensory pathways, visceral inflammation can trigger pain and/or increase the excitability of visceral afferent pathways (e.g. enhancing low threshold input into a noxious range), which can become chronic (e.g. chronic pancreatitis). Finally, while not studied in as much detail, malignancies can trigger chronic pain because of direct effects of the tumor on afferent nerves (e.g. nerve compression, release of mediators, and growth factors) or because of indirect effects, such as distension of a hollow organ.[31,32]

Clinical Implications

- Current evidence suggests that spinal afferents primarily serve the discriminatory function of nociception, which encodes the location and intensity of visceral pain. Thus treatment strategies, such as regional block or surgical dissection generally target spinal afferent pathways.
- Unilateral nerve blocks are often ineffective, which is least partly because of complex afferent innervation with sensory fibers projecting centrally on both sides in two distinct pathways.
- Visceral pain is a complex experience associated with strong emotional and autonomic reactions, which correlates with the areas activated by visceral pain and emotional processing in the anterior cingulate cortex.
- Impaired function of the viscera, such as decreased transit of material in the gut, may cause or contribute to pain because of the composition of luminal contents, increased distension, or the resulting contractions of visceral muscles. Thus effective pain management needs to consider analgesic therapies and treatment strategies targeting specific visceral functions.

Regional Block and Neural Ablation

Surgical and non-operative approaches have been developed to perform transient nerve blocks or permanently destroy the sensory pathways involved in visceral pain. Given concerns about the irreversible nature of nerve ablation or neurolysis, most studies targeting visceral sensory pathways have involved patients with inoperable cancers and relatively short life expectancies. As these patients typically present in advanced stages of their disease with poor performance status, surgical denervation plays only a minor role in the treatment. Chemical neurolysis, generally using high concentrations of alcohol or phenol, can achieve comparable results without subjecting patients to the risk of an operation. Since the first description by Kappis nearly 100 years ago,[33] several techniques have been developed to optimize the targeted delivery of neurolytic agents and minimize the likelihood of adverse effects. These approaches utilize imaging methods to guide and confirm appropriate needle placement, such as fluoroscopy, ultrasound, or computerized tomography. However, despite this wealth of literature, few systematic studies have addressed the efficacy, outcomes, or adverse effects of these interventions. Problems assessing the effects of visceral pain management with peripheral blocks are further confounded by differences in type, concentration, and amount of the neurolytic agent, primarily alcohol, in both definition and measurement endpoints and in follow up time.

Celiac Plexus and Splanchnic Nerve Block

Spinal afferents innervating organs in the upper abdomen traverse the celiac plexus with two distinct ganglia located caudal to the origin of the celiac artery. The afferents travel centrally behind the crura of the diaphragm in the splanchnic nerves. The traditional dorsal approach uses the 12th rib and spinal process of the first lumbar vertebra as landmarks.[34,35] With the patient in the prone position, a needle is advanced about 7 cm lateral to the midline at a 30–45 degree angle and tilted slightly cranially to reach the lateral wall of the body of the first lumbar vertebra. The needle was then moved anteriorly by approximately 2 cm. If aspiration does not yield blood return, water-soluble contrast (3–5 mL) often mixed with a local anesthetic is injected under fluoroscopic guidance. To better directly target the celiac plexus, the needle can be placed approximately 2 cm more anterior, which requires piercing the diaphragmatic crura and positioning the needle close to the anterolateral aspect of the aorta. Severely ill patients with respiratory compromise, patients with significant ascites, or recent abdominal surgery often poorly tolerate being in the prone position for the time required to complete this procedure. Therefore an anterior approach has been developed with the advancement of the needle from the epigastric area toward the body of the first lumbar vertebra. If the appropriate position is confirmed, a neurolytic agent, generally phenol or alcohol, is given. Current approaches mostly rely on the tissue destructive properties of alcohol, which is used in concentrations between 50%–99% and volumes between 20 and 50 mL per injection. Injections are generally performed bilaterally to destroy the afferent pathways effectively. More recent reports suggest that radiofrequency ablation may provide an alternative and perhaps better approach than chemical neurolysis.[36,37]

However, larger studies are needed to more conclusively show a clinically relevant difference between these approaches.

Various imaging techniques have been used to improve the efficacy of neurolysis and to decrease the potential for adverse effects. The celiac ganglia are too small to allow direct visualization with computed tomography (CT) scanning or transabdominal ultrasound. Using endoscopic ultrasonography, the scanner can be brought into close proximity to the plexus. However, the ganglia do not differ in echogenicity from surrounding structures; thus they do not allow direct imaging and identification of the target structure. Therefore all approaches rely on identifying the celiac artery as the main landmark. CT allows guidance of the needle to the target area and a three-dimensional reconstruction of the area affected by the neurolytic agent, based on the spread of radiopaque contrast.[38] While ultrasound allows real-time guidance without radiation exposure, air in the overlying structures often interferes with sound penetration and imaging, thus limiting its utility for patients undergoing celiac plexus block.[39] Endoscopic ultrasound with the use of an endoscopically advanced needle has been successfully used. Close inspection may identify tumor infiltration as a negative prognostic criterion and thus help in appropriate patient selection.[40] In addition, alcohol injection alters the echogenicity of the affected tissue, thus allowing direct visualization of the spread of the neurolytic agent.[41] Only one trial directly compared endoscopic and conventional percutaneous approaches in celiac plexus block, suggesting the superiority of the endoscopic approach for efficacy outcomes.[42]

Surgical Celiac Plexus or Splanchnic Nerve Ablation

One randomized controlled trial and several small case series have used surgical approaches to ablate the celiac ganglia or splanchnic nerves. Direct visualization during surgical exploration allows targeted injection of neurolytic agents into the celiac plexus if curative resection cannot be performed.[43] Because of advances in preoperative imaging, fewer patients currently undergo exploratory laparotomies, thus limiting the number of patients who might undergo an intraoperative celiac plexus block or ablation. Thoracoscopic resection of splanchnic nerves has been reported with the advent of minimally invasive surgery. As is true for less invasive procedures, approaches have not been standardized with unilateral and bilateral resection with or without vagotomy being performed to achieve pain control in these patients.[44–46]

Efficacy Of Neural Block and Ablation

Despite a wealth of published data, questions about the benefits, the best approach, and potential unintended consequences remain regarding the efficacy of neural blocks and ablation, which are likely because of differences in patient selection, interventional techniques, and outcome measures. A meta-analysis published in 1995 concluded that nearly 90% of patients with various malignancies experienced good pain relief for approximately three months after the procedure.[35] Two small randomized controlled trials demonstrated similar pain control but lower adverse effects because of decreased opioid consumption in patients treated with neurolytic block.[47,48] Subsequent studies point to a slight advantage of ablative treatment over pharmacotherapy. Intraoperative celiac plexus block with 50% alcohol led to stable pain subjective pain severity scores in patients with inoperable pancreatic cancer, while patients receiving saline injection as a control experienced a significant increase in pain scores during follow up. This improvement in pain control was associated with a significantly lower use of opioids.[43] In a posthoc analysis, patients with significant pain had improved survival if they underwent celiac plexus block, compared to controls. However, there was no overall survival benefit when the comparison was made using the original entire study cohort. Three subsequent trials comparing neurolytic celiac plexus block to analgesic therapy confirmed better pain relief after ablative therapy. In two studies, the improvement was transient with progressive recurrence of pain after about one to two months.[49,50] Most patients still required opioids, albeit at lower dosages compared to the control in the two smaller studies.[49,50] A more recent study by Wong et al. did not confirm this decrease in opioid consumption. Consistent with prior studies, their results also demonstrated that appropriate dosing of opioids achieves good pain control and quality of life that did not differ between treatment groups. However, none of these investigations demonstrated a significant effect of neurolytic plexus block on patient survival.[51] This lack of survival difference was called into question by a large study that pointed to a possible detrimental effect of celiac plexus block in pancreatic cancer patients. The retrospective design did not allow a clear answer as to why the intervention was associated with shortened survival. However, baseline characteristics suggest a selection bias with a more advanced illness stage in the group undergoing neurolysis as a potential explanation.[52] As cancer progression may affect the efficacy of ablative procedures by lowering apparent response rates, one small study randomly enrolled patients to perform early and late neurolytic blocks.[53] While both groups reported better pain control than medically treated controls, there were no significant differences between the groups, arguing against disease progression as a relevant confounder. Despite some remaining questions, these data and meta-analyses indicate that pain relief after neurolytic block in pancreatic cancer is at least comparable to conventional analgesic therapy and may be associated with lower opioid consumption and thus fewer treatment-related side effects.[54–56]

Rather than targeting the celiac plexus, one can also block or cut the splanchnic nerve, which has been compared in one trial with celiac plexus block.[57] The reported improved pain control was not consistent across key primary endpoints and was only significant for a secondary outcome measure, which was a decrease in pain intensity from baseline. Thus confirmatory studies are needed to establish whether splanchnic nerve destruction is indeed superior to the neurolysis of the celiac plexus. Similarly, the results of surgical interventions with neurolytic or neuro-ablative therapy of the splanchnic nerve remain inconclusive. While the only randomized controlled trial demonstrated good pain relief and a decrease in opioid consumption,[43] a case series evaluating different palliative operations for pancreatic cancer did not confirm a decrease in opioid use after surgery plus celiac plexus block.[58] Smaller case series reported improved pain control in about 60%–80% of patients after thoracoscopic splanchnicectomy, performed unilaterally or bilaterally with or without a vagotomy.[44–46,59–63] Poor definition of endpoints, limited assessment of analgesic effects, the lack of appropriate control groups, and the fact that comparable results were obtained using a variety of different approaches demonstrate the need for further research with rigorous methodologic design. Splanchnicectomy reduces opioid requirements compared to systemic pharmacotherapy but not compared to celiac plexus block.[46,63] Overall, the current data suggest acceptable pain relief with an at least transient decrease in opioid requirements,[54] but do

not support the superiority of one ablative approach over another. Thus the discussion of available treatment choices for patients and physicians should primarily focus on the risk/benefit ratio of the procedure, the available expertise, and whether a specific institution or provider favors one technique over others because of appropriate training and expertise in specific techniques.

Nerve Block or Ablative Therapy in Benign Disorders

Pain relief after a neurolytic block is often transient, thus decreasing the enthusiasm to use such approaches in patients with non-cancer chronic visceral pain disorders and longer life expectancies. Given this, less information is available regarding the efficacy of nerve blocks in these patient cohorts. Several case series have been published investigating the efficacy of nerve blocks in more than 500 patients with chronic pancreatitis, making this the largest patient group with benign visceral pain disease. The initial response rates to this intervention in this population varied between 30% and 90%, with limited follow up in most cases.[36,42,45,62,64–68] Because of concerns about the use of neurolytic agents, the largest series combined bupivacaine with triamcinolone.[65] While about half of the patients reported an initial benefit, sustained analgesic responses after 24 weeks were seen in only 10% of cases. The commonly practiced addition of corticosteroids has been addressed in a randomized controlled trial, which showed no additional benefit of triamcinolone with response rates of approximately 15% one month after celiac plexus block with bupivacaine plus placebo or the steroid.[69] Moore et al. reported results of stellate ganglion and paravertebral blocks with bupivacaine in 59 patients with refractory angina because of coronary artery disease.[70] About 60% of the patients reported pain relief for more than two weeks. However, the benefit was transient, and most patients required multiple interventions to maintain some benefits. Interestingly, limited experience with differential neuraxial blocks suggests that primarily visceral pain was present only in about one-fifth of patients with chronic pancreatitis, with the majority experiencing "central pain," defined by persistent pain despite surgical anesthesia through epidural administration of lidocaine.[71] Overall, the data highlight the complex etiology of chronic pain syndromes in patients with benign visceral pain disorders and do not support the use of ablative therapies in these patients.

Pelvic Nerve Blocks

Several surgical and non-operative approaches target ganglia or nerve structures projecting to the pelvic structures. The most extensive experience with appropriately designed clinical trials addresses the management of dysmenorrhea and pelvic pain in endometriosis, largely relying on presacral neurectomy or laparoscopic uterosacral nerve ablation (LUNA). Three randomized controlled trials did not show a true benefit when the nerve ablation was added to the surgical treatment of endometriosis.[72–74] Less is known about the impact of presacral neurectomy, which reportedly leads to lasting pain relief in more than 50% of patients described in a large case series.[75,76] Two randomized trials showed inconsistent results with one group reporting complete resolution of pain in 85% vs. 57% of women treated with and without neurectomy, respectively,[77] while an earlier trial concluded that only menstrual pain, but not other forms of the more chronic pelvic pain, improved after surgical nerve ablation.[78] A meta-analysis of published data did not find sufficient evidence supporting the benefit of ablative therapies in dysmenorrhea or chronic pelvic pain.[79]

Various non-operative approaches have been developed to block or ablate afferent pathways that contribute to pelvic pain. As described earlier, the pelvic viscera conveys sensory input through two distinct spinal afferent pathways, which project to the thoracolumbar and lumbosacral segments of the spinal cord. The thoracolumbar afferents give rise to the splanchnic and hypogastric nerves, while the lumbosacral afferents form the pelvic nerve. Several distinct ganglionic structures form and are potential targets for interventions. They include the inferior mesenteric and major pelvic ganglion, as well as the presacral ganglion impar. In addition, the pudendal nerve functions as the primary sensorimotor nerve for the pelvic floor muscles, sphincters, perineum, and genitals. As is true for interventions targeting the celiac plexus, options include interventions guided by cross-sectional imaging, mostly with CT, and fluoroscopic guidance relying on bony structures as landmarks. The indication and performance of the aforementioned nerve blocks depend on the affected nerves, location of the pain, technical expertise, and availability of the equipment. Current data do not show effects on success rates.[80–85]

Adverse Effects of Neurolytic Block

Acute side effects are largely related to the typical complication of invasive procedures or operations and involve injury of neighboring structures, most importantly blood vessels, infections, thromboembolic complications, and pain. Transient pain is the most common side effect of neurolytic agents. While the use of local anesthetic prior to alcohol injection decreases the incidence of this adverse effect, at least 10%–30% of patients experience significant pain within the first hours after the procedure.[39,86–88] The destruction of sympathetic efferent pathways causes vasodilation of splanchnic vessels, resulting in hypotension in up to 20% of patients.[49,86,87] Similarly, the unopposed parasympathetic drive can lead to diarrhea, which has been reported in approximately one-fifth of patients.[47,49,87,88] Pelvic nerve blocks or ablations can trigger constipation or interfere with bladder emptying. These problems can generally be managed medically with appropriate premedication, hydration, post-procedural observation, and appropriate symptomatic therapy.

For procedures targeting the celiac plexus, the posterior approach may traverse the kidney and the pleural space, potentially leading to hematuria or pneumothorax.[34,35,88] The anterior approach requires advancing the needle dorsally and potentially passing through the liver, stomach, or colon. While this is largely inconsequential, clinically relevant perforations can occur and may be difficult to diagnose because of the neurolytic block and often concomitantly administered analgesia.[89] Therefore patients should be well hydrated, receive an intravenous fluid bolus prior to performing the nerve block, and remain under observation for at least 2–4 h after the procedure. The delivery of neurolytic agents near major vessels is another potential source of complications. In all cases, aspiration should ensure that the needle is not inside the vessel before the neurolytic agent is injected. Nonetheless, indirect effects, such as mesenteric venous thrombosis, may rarely occur despite these precautions.[90] Spread of the neurolytic agent within the retroperitoneal space with lumbar nerve injury has been reported.[35] Paraparesis is the most feared and mostly irreversible complication, which is thought to be caused by injury to the nutrient vessels supplying the spinal cord.[34,35] While sufficiently powered studies addressing the likelihood of these adverse effects are not available, current evidence suggests that the incidence does not differ between the different approaches.[41,63,87]

Clinical Implications

- Neurolytic celiac or splanchnic nerve block is a moderately effective method to decrease pain in patients with intra-abdominal malignancies and has been best studied in patients with pancreatic cancer. The benefit is often transient and may decrease the need for opioids but does not clearly affect life expectancy or quality of life compared to conventional pain management.
- Pelvic nerve blocks or ablations can at least transiently relieve chronic pelvic pain but have inconsistent effects when assessed over longer periods of time. Adverse effects are largely minor and transient and can be managed by appropriate medical therapy. Approaches using different imaging techniques or even direct operative treatment do not seem to affect the outcome or incidence of side effects.

Central Treatment Targets for Visceral Pain

Epidural block or pharmacotherapy, spinal cord stimulation, and surgical myelotomy have been used to treat chronic visceral pain syndromes. Two aspects unique to visceral pain syndromes warrant a specific discussion of spinal treatment targets. First, preliminary studies suggest that patients with ischemic heart disease may derive significant benefits from epidural blocks. Second, unlike non-visceral pain, which is primarily relayed to supraspinal sites via the spinothalamic tract, functional and neuroanatomic studies have demonstrated that the dorsal column ascending pathway plays an important role in visceral pain.[91,92] Considering these points and the complex innervation of visceral structures, we cannot extrapolate from studies that focused on spinal approaches to manage non-visceral pain. Unfortunately, only a few studies have systematically evaluated the clinical efficacy of these approaches over long periods, thus limiting their ability to fully assess their therapeutic value.

Epidural Analgesia and Visceral Pain

Spinal drug delivery through epidural catheters allows the delivery of opioids and other agents without a significant risk of systemic adverse effects. Acute or chronic epidural drug delivery alleviates visceral pain in patients with cancer-related pain and some patients with non-cancer pain disorders.[71,93] Interestingly, high thoracic epidural anesthesia significantly improved angina in patients with refractory pain because of coronary artery disease and decreased documented episodes of cardiac ischemia as judged by ST depressions.[94,95] A more recent study provided further insights into the underlying mechanism by demonstrating improved cardiac perfusion during high epidural analgesia, likely because of a concomitant block of sympathetic pathways.[96] While a case series suggested a lasting improvement over periods of more than one year,[97] a small controlled trial randomized patients to saline or bupivacaine and did not see differences in pain control.[98] Epidural analgesia plays a role in perioperative pain control during and after abdominal and pelvic surgeries. It may also help in differentiating peripheral from central pain mechanisms and may thus allow the selection of patients who are more likely to respond to peripheral nerve blocks.[99] Information addressing a more chronic use of epidural pain pumps for chronic abdominal or pelvic pain is limited to isolated case reports, thus not allowing an assessment of efficacy. Independent of questions about benefits, safety issues have not been addressed but will likely be similar to the previously reported complication rate of epidural drug delivery, which is addressed in more detail in a separate chapter.[100–102]

Spinal Cord Stimulation and Visceral Pain

Recently, several case reports have described significant improvements in severe visceral pain with spinal cord stimulation. The largest series compiled data from a total of 70 patients with refractory thoracic, abdominal, or pelvic pain syndromes.[103] Less than 10% did not respond to the temporarily implanted trial electrodes; responders to the trial were then offered a permanent device, which was surgically implanted and led to a maintained improvement with lower opioid requirements in the majority of patients. Two single-center studies focused on patients with chronic pancreatitis and noted a benefit for up to one year in about 80% of the patients.[104,105] However, data were analyzed retrospectively and relied on physicians rather than patient ratings. Finally, complications such as lead migration and device removal have been shown to be as prevalent as 10%–20% and are important caveats that show the need for controlled studies before more broadly introducing this approach into clinical practice. Only one small trial randomly allocated patients with IBS to active treatment or no stimulation in a crossover design. While the lack of an appropriate control intervention leaves questions when testing the effects of an active therapy that can be easily felt, patients experienced less pain during stimulation only.[106] While not targeting the spinal cord, sacral neuromodulation may be effective in chronic pelvic pain. Using an approach that has been approved for the treatment of voiding dysfunction, sacral neuromodulation stimulates the afferent sacral roots through transforaminal implanted electrodes. Meta-analyses included assessments of pain ratings as secondary endpoints and reported improvement.[107,108] However, the degree and duration of this improvement require more detailed data,[109] especially as approximately half of the patients have reinterventions within the first few years, and about 30% will eventually have the device removed.[110,111]

Myelotomy and Visceral Pain

Since its introduction more than 20 years ago, midline myelotomy has been used to treat patients with refractory pain because of visceral malignancies.[112] Open surgical and percutaneous CT-guided approaches have been developed. However, the nature of this intervention as a "rescue" treatment in patients who failed other therapies limits information to small case series and does not allow us to judge its clinical efficacy. Case series are typically limited to patients with advanced malignancies and report improved pain control in about 60% of patients, with symptoms reoccurring in up to half of the patients.[113–116]

Transcutaneous Stimulation

The search for non-invasive treatments and the reported benefit of transcutaneous electrical or magnetic stimulation techniques in non-visceral pain led to the use of these therapies in some visceral pain syndromes. While these techniques are available and, in the case of transcutaneous electrical nerve stimulation (TENS), a part of routine pain management, published data supporting their utility in visceral pain remain limited. TENS improved angina threshold and exercise capacity in patients with coronary artery disease, with an inconsistent effect on pain severity.[117,118] Only one small study of healthy volunteers tested TENS on acute experimental pain

originating in the gut and reported that TENS led to a higher pain threshold during esophageal distension.[119] Similarly, electroacupuncture decreases the sensation of rectal distension in healthy persons.[120] However, it is unclear whether the blunted responses to acute experimental pain in healthy persons indeed translate into a relevant benefit for patients with chronic visceral pain.

Repetitive transcranial magnetic stimulation over the motor cortex showed some initial promise in various disorders characterized by chronic pain.[121] A small blinded crossover trial showed the benefit of active therapy in patients with chronic pelvic pain.[122] While a meta-analysis suggested a possible short-term benefit of this approach to chronic pain independent of locus or presumed mechanism, the authors did not see lasting effects and withheld more conclusive support for this modality because of concerns about bias.[123]

Clinical Implications

While systematic studies have not specifically addressed the efficacy of epidural drug delivery in patients with chronic visceral pain syndromes, currently available data support its use in patients with refractory pain because of ischemic heart disease. Data on spinal cord stimulation or myelotomy remain limited to uncontrolled and often small studies, which suggest a potential, albeit often only partial and transient pain relief, and should be reserved for patients with intractable pain because of terminal disease. Theoretically, non-invasive modalities that rely on transcutaneous electric or magnetic stimulation lack proven efficacy in visceral pain.

Mechanism-Oriented Pharmacotherapy of Visceral Pain

Visceral pain is often associated with abnormalities in organ function, such as constipation, nausea, cardiac failure, or dysuria. These abnormalities may cause or contribute to pain or be caused by pain syndrome or its treatment. Thus the evaluation of patients with visceral pain syndromes should always go hand-in-hand with appropriate functional assessment of the affected organ system(s). Selectively altering these functions may offer options to alleviate discomfort without relying on analgesic agents or interventions that specifically target sensory mechanisms.

Serotonin and Gastrointestinal Pain Management

As described above, the gastrointestinal tract contains 95% of the body's serotonin (5-HT), which is involved in many different functions. Neurons, smooth muscles, and epithelial cells express different serotonin receptors. The ligand-gated 5-HT_3 receptor has been found on vagal and spinal afferents and is involved in visceral sensation, including the perception of nausea.[124,125] Metabotropic 5-HT receptors exert more complex effects on gut function as they act on multiple targets, including muscle and nerve cells, with limited studies suggesting that 5-HT_4 agonists and 5-HT_1 antagonists may decrease visceral sensation in experimental animals and healthy volunteers.[126–128] Currently, selective 5-HT_3 receptor antagonists and 5-HT_4 receptor agonists are available for clinical use. While there is some experience with other serotonin receptor blockers, this experience is limited, mostly demonstrating physiologic changes in healthy controls or short-term effects in patients with mild abdominal discomfort. Anti-depressants alter serotonin signaling, mostly by inhibiting the reuptake mechanism that terminates the effect of the released serotonin and is commonly used in patients with various pain syndromes, including those with visceral pain. Considering their significant impact on central processing, it is impossible to attribute the effects to peripheral changes in serotonin signaling.

Clinical Efficacy of Serotonin Agonists and Antagonists

The 5-HT_3 antagonist alosetron has been successfully used in patients with functional bowel disease, characterized by abdominal pain and diarrhea.[129–132] However, the effect is relatively modest, with a recent meta-analysis showing a small odds ratio (1.8) favoring the active agent over placebo, translating into a number needed to treat of about 7.[133] Other 5-HT_3 receptor antagonists, such as ondansetron, play an important role in the treatment of severe nausea and vomiting but show some efficacy in diarrhea as well with less consistent effect on pain.[124,134–137] The variable impact on pain fits the results of preclinical studies that argue against a direct analgesic effect of these agents.[138] Tegaserod, a 5-HT_4 receptor agonist, significantly accelerates gastrointestinal transit and alleviates symptoms of constipation, including associated discomfort and pain.[139,140] Using global improvement scores, currently available data suggest a relatively low odds ratio (2.0) favoring tegaserod over placebo with a number needed to treat about seven.[141] Tegaserod had been removed from the market in the United States because of safety concerns and recently received approval limited to women under 65 years with chronic constipation. Another 5-HT_4 receptor agonist, prucalopride, improved constipation with an associated increase in quality of life indicators, including abdominal bloating and discomfort. However, the limited information suggests an indirect benefit because of improved constipation rather than a direct analgesic effect.[142,143]

As already mentioned, most anti-depressants affect serotonin signaling, with selective serotonin reuptake inhibitors (SSRIs) being the most commonly used agents. Many studies have addressed the impact of anti-depressants on visceral pain, primarily focusing on gastrointestinal disorders. While individual studies have discrepant results,[144–146] recent meta-analyses suggest improvement of functional gastrointestinal disorders, but not as clearly in pelvic pain.[147–150] Interestingly, there is no clear difference between the less specific tricyclic anti-depressants and agents that selectively interfere with serotoninergic signaling, arguing against a pathway-specific effect. Similarly, it is unclear whether we are truly dealing with changes in pain sensations. For SSRIs, the improvement was primarily because of changes in global assessment scores rather than pain ratings. Considering the potential impact of psychiatric comorbidity as a confounder, one study specifically examined the effect of citalopram in non-depressed patients with IBS and did not demonstrate any benefit.[151] While a case series described cohorts treated with other agents, only one serotonin-norepinephrine reuptake inhibitor, venlafaxine, has been appropriately examined in patients with dyspepsia as a disorder associated with pain and was not superior to placebo.[152] Two small studies examined duloxetine in combination with an α-receptor blocker in chronic prostatitis and pelvic pain, with results suggesting beneficial effects on pain and quality of life.[153,154] Overall, currently available data support the use of anti-depressants, preferentially tricyclics and SSRIs, in functional gastrointestinal disorders associated with pain, especially in patients with coexisting anxiety or depression.

Adverse Effects of Serotonin Agonists and Antagonists

The most common side effect of alosetron and related agents is constipation, which is reported in 20%–40% of patients.[141] Alosetron has been linked to ischemic colitis, a potentially fatal disease, which led to its withdrawal from the market.[133] It is currently only available under a restricted access program with stringent monitoring. Tegaserod use has also been associated with ischemic events, in this context myocardial infarction, and was similarly removed from the market but was recently made available again with a more restricted indication.

Smooth Muscle Relaxants and Visceral Pain

Stretch and tension are stimuli that are adequate to evoke conscious visceral sensation, corresponding to distension of a hollow viscus or contraction of the tunica muscularis.[30] The visceral muscle is morphologically and functionally distinct from striated muscle, thus potentially allowing the use of pharmacologic interventions that may not significantly affect striated muscle. Several strategies have emerged or are currently under investigation. Most rely on the blockade of muscarinic receptors, the main excitatory signaling mechanism between parasympathetic neurons and visceral smooth muscle. Less commonly used strategies employ agonists for α-adrenergic receptors or L-type calcium channel blockers to affect the contractility of the visceral smooth muscle. The latter two approaches have largely been used in healthy volunteers, showed only limited efficacy in small studies involving patients with different painful disorders, and carry a significant risk of adverse effects, primarily symptomatic hypotension.[155–160] Therefore the discussion of spasmolytic agents will focus on muscarinic receptor antagonists, such as hyoscyamine or dicyclomine, with the best evidence emerging from studies performed in patients with functional diseases of the gastrointestinal tract.

Clinical Efficacy of Smooth Muscle Relaxants

Two published meta-analyses concluded that compared to placebo, patients receiving anticholinergic drugs are twice as likely to report an overall benefit, which includes pain relief.[161,162] However, many of the patients experienced relatively mild pain at baseline with only moderate pain relief compared to placebo.[147]

Adverse Effects of Smooth Muscle Relaxants

Approximately 10% of patients experience largely minor adverse effects, mainly because of effects on mucous membranes, the urinary tract and eye, dry mouth, urinary retention, and problems with accommodation. Based on the mechanisms of action, anticholinergic drugs are contraindicated in patients with known glaucoma and should be avoided in patients with micturition problems.

Botulinum Toxin and Visceral Pain

The clinical use of botulinum toxin has expanded significantly beyond the initial target, spastic motor disorders of skeletal muscles.[163] More than 15 years ago, it was shown to affect smooth muscle as well, leading to symptomatic improvement in patients with achalasia.[164] As anecdotal evidence suggested a decrease in pain independent of its effect on muscle activity, botulinum toxin has been increasingly used to treat various pain syndromes, presumably by directly altering peripheral transmitter release from nociceptive afferent nerve terminals.[165] Essentially, all the studies focusing on patients with visceral pain are case series. Patients often present with associated impairment of visceral function, such as dysphagia, gastroparesis, or voiding dysfunction. Considering the likely impact of the agent on muscle activity, it is impossible to differentiate the direct effects on afferent pathways from the results of improved organ function.

Clinical Efficacy of Botulinum Toxin

Few studies have focused on pain and have systematically examined changes in pain intensity after treatment with botulinum toxin type A. In patients with various esophageal motility disorders characterized by pain, injection of botulinum toxin into the distal esophagus significantly reduced the pain score from severe to mild in approximately two-thirds of patients for about five months.[166] In a smaller case series of patients suffering from diffuse esophageal spasm with severe chest pain, endoscopically guided injection of botulinum toxin along the tubular esophagus resulted in nearly complete alleviation of pain for six months.[167] There are limited results about the effects of botulinum toxin in other areas of the gastrointestinal tract, suggesting a potential benefit in disorders associated with pain.[168] In the urinary tract, botulinum toxin has been successfully used to treat voiding disorders. While a case series suggested some effect in painful bladder syndrome, an idiopathic disorder characterized by pelvic pain, urinary urgency, and increased frequency of micturition, results of randomized controlled trials are inconsistent with larger trials that do not confirm superiority over placebo.[169–172] In contrast, smaller single-center studies suggested a potential benefit.[173–175]

Adverse Effects of Botulinum Toxin

Generally, low doses of locally injected botulinum toxin do not cause systemic side effects. Adverse effects are largely limited to transient pain or infectious complications at the injection site, such as urinary tract infections. Injection close to the striated muscle, most notably the sphincteric muscle for the bladder or rectum, may lead to transient incontinence.

κ-Opioids and Visceral Pain

Opioids are potent analgesics for non-visceral and visceral pain. However, μ-opioid receptor agonists commonly cause gastrointestinal side effects, such as nausea, vomiting, and constipation. These unwanted effects may become dose-limiting, especially in patients with gastrointestinal disorders. In addition, the rising incidence of opioid addiction with the associated deaths because of overdoses has led to increasing concerns about the use of these agents in benign disorders. As peripheral visceral afferents express κ-opioid receptors, κ-agonists have been developed to take advantage of their analgesic properties and a lower likelihood of adverse effects.[176] Animal and acute studies in human volunteers demonstrated increased thresholds to painful visceral stimuli, consistent with a potential analgesic effect.[177,178] However, central effects with significant dysphoria limit the use of κ-agonists to peripherally acting agents.

Clinical Efficacy of K-Opioid Agonists

A single small study reported κ-agonist-induced pain relief in patients with chronic pancreatitis who were refractory to μ-opioid agonists. However, patients have only been studied acutely after a single administration of the agonist.[179] Several randomized controlled trials examined the effects of fedotozine, a κ-opioid agonist, in patients with chronic abdominal pain because of functional disorders over two to six weeks, with two of the studies suggesting a small benefit compared to placebo.[180–182] On-demand therapy with asimadoline, a peripherally acting κ-opioid agonist, did not affect pain severity in patients with IBS.[183]

The recently introduced eluxadoline has a complex effect on opioid receptors, functioning as an agonist on μ-and κ-opioid receptors and as an antagonist of δ-opioid receptors. At the recommended dosages, the effects were peripherally restricted. The agent has been approved in the United States for the treatment of diarrhea predominant IBS based on the improvement of a composite endpoint that included improved bowel patterns and pain relief.[184] True visceral analgesic responses independent of the potential indirect effects on intestinal function have not been assessed.

Adverse Effects of K-Opioid Agonists

Randomized controlled trials did not report a significantly higher incidence of adverse effects after administration of peripherally acting κ-opioid agonists than placebo.[141] Eluxadoline may affect the sphincter of Oddi and has been linked to cases of acute pancreatitis with fatal outcomes.[185] As such adverse responses are more common after prior cholecystectomy, the agent should be avoided in patients without a gallbladder.

Agents Targeting the $\alpha_2\delta$ Calcium Channel Subunit

Voltage-sensitive calcium channels play an important role in neuronal excitability and transmitter release. Gabapentin and pregabalin were initially developed as anti-convulsive agents. As changes in neuronal excitability and synaptic plasticity are known to contribute to peripheral and central sensitization, both agents have been used in patients with chronic visceral pain. In healthy volunteers and patients with IBS, these two medications were shown to blunt acute pain triggered by rectal distension.[186,187]

Clinical Efficacy of Agents Targeting The $A_2\Delta$ Subunit

Despite the changes in acute pain sensitivity, pregabalin was not superior to placebo during a two week course of treatment in patients with IBS.[187] A more recent investigation suggested improvement in pain severity but no significant benefit in the global assessment of relief or impact on quality of life.[188] Consistent with the reported impact on pain, another study showed improved pain control and decreased opioid use in patients with chronic pancreatitis treated with pregabalin.[189] A second study combined antioxidants with pregabalin in a cohort of patients with chronic calcific pancreatitis, showing a more significant and lasting pain relief when compared with placebo.[190] Inconclusive results emerged in studies testing these agents for patients with chronic pelvic pain. Pregabalin was not superior to placebo in the treatment of chronic prostatitis.[191] A small trial of gabapentin did not report a clear benefit in pelvic pain,[192] which contrasts with a more recent single-center trial in women that showed improved pain control.[193]

Adverse Effects of Agents Targeting The $A_2\Delta$ Subunit

Overall, gabapentin and pregabalin were well tolerated, without serious adverse events. However, patients may report edema and problems with cognition and balance, often citing feeling as if drunk.

Clinical Implications

Improved understanding of normal visceral function and sensation has led to the development of new therapeutic strategies. In the gastrointestinal tract, muscarinic receptor antagonists, serotonin receptor agonists, and antagonists alter function and may improve the discomfort associated with functional disorders. Anti-depressants are commonly used and may improve the global symptom score, likely because of their effect on often coexisting psychiatric illnesses. A recent study in patients with chronic pancreatitis suggested the efficacy of pregabalin in visceral pain. Several targeted treatments are currently under development using drugs that interact with purinergic receptors and members of the family transient receptor potential channels (TRPV1 or TRPA1).

Luminal Contents and Visceral Pain

Within the last decade, the microbiome has attracted significant interest because of the complex interactions between ingested foods, the microbial flora with its metabolic activities and breakdown products, and the gut may lead to changes in gastrointestinal function, which could contribute to pain. While there may be emerging differences between control populations and persons with IBS, there is significant heterogeneity between studies. More importantly, many patients with gastrointestinal problems alter their dietary habits, which will indirectly affect microbial colonization of the gut, thus leaving us with the question of whether these shifts indeed play a pathogenic role or are driven by the disease and its impact on behaviors, such as food choices.[194] Mechanistic studies suggest a causal role, as the changes in the microbiome are associated with other changes in luminal contents, such as higher protease activity, which can affect gut functions, such as epithelial permeability and sensory function, and thus lead to pain.[195,196] While still inconclusive, these findings prompted studies that alter the microbiome, mostly focusing on patients with IBS. Simple interventions with probiotics that try to modify the microbial colonization of the gastrointestinal tract may provide some relief in diarrhea predominant IBS, with inconclusive data because of variable design and inconsistent results.[197] Conversely, the use of a poorly absorbed antibiotic for two weeks decreased overall symptom severity and lowered discomfort ratings.[198] However, about two-thirds of the responders relapsed within 18 weeks,[199] raising questions about the appropriateness of such a strategy in the context of a typically chronic benign illness and increasing concerns about antimicrobial resistance. A small open-label study targeted a more comprehensive and perhaps lasting change by performing fecal microbiome transfers in a small cohort,

which led to significant benefit.[200] While promising, published data remain sparse and inconclusive, with studies using different endpoints and different methods in often small patient cohorts.[201] Despite the preliminary nature of these results, the interactions between host and microbiome affect the gut function and directly or indirectly influence more distant body areas. As our understanding of these complex interactions evolves, we will likely see more targeted interventions that could affect pain perceptions in areas beyond the gut.

Distension of the hollow viscera is associated with conscious perception and pain and may contribute to discomfort associated with disorders, such as constipation. Experimentally induced constipation indeed triggers pain in healthy volunteers.[202] Conversely, recently introduced secretagogues, such as linaclotide, plecanatide, or lubiprostone, alleviate constipation and decrease pain.[203–205] Specific pathways have been invoked to explain this decrease in pain, and meta-analyses suggest a more indirect effect because of the laxative effects of these agents.[206]

TABLE 41.1 Summary of Interventions Targeting Visceral Pain. Invasive and Non-Invasive Treatments are Listed if Their Use had been Investigated by Randomized Clinical Trials (Rct) and/or Meta-Analysis (Ma)

	EVIDENCE			
Approach/Agent	RCT	MA	Clinical Use	Comment
INTERVENTIONS TARGETING PERIPHERAL PATHWAYS				
Celiac Plexus Block				
-neurolytic	+	+	Pancreatic cancer	Transient effect
-bupivacaine	+/–		Chronic pancreatitis	
Laparoscopic uterosacral nerve ablation	–		Pelvic pain, endometriosis	
Presacral neurectomy	+/–	–	Pelvic pain, endometriosis	
Sacral neuromodulation		+	Pelvic pain	Frequent reoperations
INTERVENTIONS TARGETING THE BRAIN				
Transcranial magnetic stimulation	+	+/–	No specific area	Transient effect, concerns about bias
Psychological treatments	+	+	IBS, functional dyspepsia, functional abdominal pain	
PHARMACOTHERAPY				
Botulinum toxin	+/–		Painful bladder syndrome	Impact on micturition
Serotonin signaling				
-Alosetron	+	+	IBS-D	Approved for women
-Ondansetron	+/–		IBS-D	Off label use
-Tegaserod	+	+	IBS-C	
-Prucalopride	+	+	IBS-C	
Spasmolytics	+	+	IBS	
Secretagogues				
-lubiprostone	+	+	IBS-C	
-linaclotide/plecanatide	+	+	IBS-C	
Probiotics	+/–	–	IBS	Marginal effect in IBS-D
Rifaximin	+	+	IBS-D	High recurrence rate
Eluxadoline	+	+	IBS-D	Pancreatitis risk
Gabapentin/pregabalin	+		Pancreatitis	Marginal pain relief
	+/–	–	Pelvic pain	
Anti-depressants				
-Tricyclic Anti-depressants	+/–	++	IBS, functional dyspepsia, pelvic pain	
-SSRI	+/–			
-SNRI	+/–			

IBS, Irritable bowel syndrome (D-diarrhea predominant; C-constipation predominant); *SSRI*, selective serotonin reuptake inhibitor; *SNRI*, serotonin-norepinephrine reuptake inhibitor.
Evidence Supporting Efficacy is Shown by Symbols and Classified as Beneficial (+) or Ambiguous (+/-)

Psychological Interventions and Visceral Pain

Expert consensus and meta-analyses consistently support the utility of psychological treatment approaches in persons with visceral pain syndromes, which range from cognitive behavioral therapy to mindfulness and hypnotherapy.[207] The main caveats are cost, insurance coverage, and availability, which can be overcome by offering group treatments, lowering the number of direct patient encounters, or relying on remotely directed treatments with virtual or telephone encounters. Such approaches have been tested and seem to be effective.[208–210] Alternatively, limited resources can be focused on groups that are more likely to benefit from these interventions, which could reduce societal costs without reducing the financial burden for individuals using these treatments. While we still have limited insight into potential predictors of treatment success, published data suggest that overall symptom severity, trait anxiety, and anxiety sensitivity at baseline are associated with a higher probability of response to treatment.[211,212]

Conclusion

Visceral pain poses unique diagnostic and therapeutic challenges. Clinicians need to consider the complex interactions between organ function, pain, and pain management when deciding on treatment. Frequently used interventions may be effective in altering organ function rather than directly blunting pain. Beyond an increasing number of medical treatment options, psychological therapies should play a bigger role, especially as novel approaches with remote encounters and shorter treatment courses lower barriers because of availability or cost constraints. Invasive procedures or operative interventions should be reserved for refractory cases. They can at least transiently alleviate pain but do not consistently improve the overall quality of life compared to conventional treatments (Table 41.1).

Key Points

- Visceral afferents have complex innervation with bilateral projections of the spinal and vagal pathways to most organs.
- Visceral input is typically poorly localized and may not accurately differentiate between distinct stimulus modalities and projects to distant dermatomes ("referred pain").
- Visceral pain is associated with strong emotional responses and may thus have a more negative impact than pain triggered in other body areas.
- Treatment of visceral pain with medical and interventional techniques may alter organ function, which can affect the sensation and pain of these structures.
- Epithelial structures and luminal contents can activate visceral sensory pathways and contribute to visceral sensation and pain. Interference with these signaling pathways may alleviate pain.
- Hollow organ distension and contraction can be perceived and can lead to pain. Altering filling status or contractile activity should be considered in the management of pain involving the gastrointestinal tract, bladder, or uterus.
- The human microbiome is emerging as another potential factor that can modify visceral afferent input and perception and may thus be a target for treatment steps.

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Pelvic Pain

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Introduction

Approximately 10% of people in the United States are living with pelvic pain. Many pain specialists, experts in their fields and adept at managing boundaries of care, decline referrals for pelvic pain. Nevertheless, the pain specialist skilled at differential diagnosis and collaboration is best positioned to impact the outcome in these patients. In this chapter, we outline the differential diagnosis, discuss workup and evaluation, and provide straightforward tools to effectively treat, or at least triage in an impactful manner, the majority of those presenting for treatment of pelvic pain. For completeness, we will also discuss rectal and anal pain.

Most definitions of chronic pelvic pain (CPP) describe a three-to-six-month duration. The American College of Obstetrics and Gynecology (ACOG) states that CPP can be intermittent or constant and persists for at least six months.[1] The European Association of Urology defines CPP as "chronic or persistent pain perceived in structures related to the pelvis of either men or women." They point out that "it is often associated with negative cognitive, behavioural, sexual, and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction."[2] A chronic pelvic pain syndrome refers to "the occurrence of CPP when there is no proven infection or other obvious local pathologic condition that may account for the pain." In the United States, 15% of females indicate they have experienced either constant or intermittent pelvic pain during the preceding six months.[3] CPP of three months' duration is present in 8.2% of males. Special circumstances may surround children, transgender individuals, or those with disabilities.[4]

Herein lies the frustration for pain specialists: pelvic pain can derive from urologic, gynecologic, gastrointestinal, musculoskeletal, neurologic, and/or rheumatologic causes and can manifest in the setting of significant psychological and social confounders. The most important strategy is to approach pelvic pain as a multidisciplinary issue. Potential causes should be sought by the appropriate specialists and addressed if found. If no particular cause is identified, the goals are to manage symptoms and provide coping strategies. Given the patient complexity, it is essential to structure the patient evaluation for efficiency and completeness.

To optimize face-to-face provider time, the patient should be given tools to describe symptoms, an inventory on which to keep track of prior evaluations and treatments, and provided with resources to read on their own, such as *Facing Pelvic Pain*, a recent multi-disciplinary publication aimed at the lay public, containing the data inventory the "treatment map."[5] This tool both empowers the patient and reduces work for the team of providers. With the details in hand, the pain specialist can then ask the patient to tell their story, begin formulating the differential diagnosis, and develop a sound treatment plan.

The pain specialist can have a longstanding impact on those with CPP by employing the most basic of tools to start the patient off on the right path:

1. In early, localized cases, the history almost always leads to the differential diagnosis. For example, if pelvic pain began subsequent to gait alteration (e.g. bunion surgery), consider pelvic floor muscle hypertonicity, and treat with physical therapy. Pelvic pain that appeared acutely three months prior with lower urinary tract symptoms and occasional flank pain may simply be a ureteric stone lodged within the section of the ureter traversing the bladder.
2. A physical exam can reveal obvious clues, such as vulvar and perineal varices
3. suggesting pelvic venous congestion or an altered gait and muscle atrophy suggestive of a sacral tumor.
4. In later more complex cases, the comprehensive review of a patient's prior medical records will lead to the most efficient care, but the history is still the essence of a successful outcome. In these complex cases, the pelvic health history form published by the international pelvic pain society or the treatment map from *Facing Pelvic Pain* completed in advance of the visit can save a great deal of time in the clinic.[5,6] An example of complex localized pain might be a patient in her mid-20s with psychological overlay whose bladder and pelvic pain began at 14 years in the setting of a traumatic childhood. Many trials later, fecal symptoms and calf atrophy on exam may lead to the diagnosis of tethered spinal cord.
5. Patients who present with multiple chronic overlapping pain syndromes (COPCs), e.g. pelvic pain, irritable bowel syndrome, migraine, gastroesophageal reflux, tinnitus, and dizziness, may have a systemic issue such as small fiber polyneuropathy, or central sensitization (alterations in the central processing of pain). Certain brain regions or connectivity among brain regions (such as cingulate, insular, and prefrontal cortices) related to pain modulation are shown to be dysfunctional in chronic pain conditions. It may also be that mechanisms driving peripheral sensitization could be present in the CNS or impact the CNS through an impact on the "pain memory." These patients will

benefit from a referral to pain management and/or a neurologist with experience in autonomic dysfunction, or in the case of a rheumatologic symptom array, a rheumatologist.
6. Curate a multi-disciplinary list of urologists, gynecologists, gastrointestinal and colorectal specialists, rheumatologists, neurologists, neurosurgeons, pelvic floor physical therapists, and alternative medicine specialists who will earnestly work with the patient's needs and who will support you in the patient's management.
7. Set expectations from the beginning as to the role of the pain specialist *vis-a-vis* the rest of the team. CPP should only rarely lead to urgent phone calls.
8. Provide backup plans, so the patient does not have as much opportunity to become anxious when pain levels are high. These might range from warm baths and heating pads to rescue medications to asking the primary care doctor to order standing culture orders.
9. The above are all straightforward strategies the pain specialist can use to deeply impact care without knowing a great deal about pelvic pain. Beyond this baseline, the more one knows, the more interesting the population becomes. People with pelvic pain have a high potential for diagnosis, cure, treatment, and management in unique and satisfying ways, especially when prior providers have not served their needs.

Causes of Pelvic Pain and Initial Evaluation

Pelvic pain can originate from virtually any organ system within the human body.[7] This is true in both acute and chronic causes of pelvic pain. Sometimes a single diagnosis can be made, such as constipation, but pelvic pain is often because of a combination of disorders as neighboring organs become sensitized.[8] When psychological and social confounders are present, identifying the cause of pelvic pain can remain a challenge for even the most experienced clinicians, and collaboration with psychology/psychiatry is essential. Some sources cite endometriosis and pelvic venous disorders as the most common causes of CPP, but it is important to note that many patients with CPP remain without a specific diagnosis.[9] One study performed in the United Kingdom reviewed 483 patients with CPP; the most common diagnoses were irritable bowel syndrome (IBS) (19.8%), psychological (9.5%), ovarian cyst (8.4%), endometriosis (7.4%), interstitial cystitis (7.2%), and pelvic inflammatory disease (PID) (6.5%).[10] Only about 50% of the 483 patients received a diagnosis. A study conducted in New Zealand obtained similar results.[11] Findings like these highlight the difficulties in managing pelvic pain and the need for a coordinated, multi-disciplinary approach, especially since it has been shown that delay in treatment can lead to greater pain sensitivity and involvement of other organs.[12]

There are several ways to approach a person presenting with pelvic pain as etiologies can be grouped in different ways: according to location, organ system, sex, or even age. Tables 42.1 and 42.2 show location and organ system involvement, respectively, along with possible etiologies.

It has been reported that 55%–80% of all diagnoses in the primary care setting are made after the history taking and physical examination.[13,14] This fact can provide confidence when approaching the history and initial evaluation of pelvic pain.

History should assess obstetric, gynecologic, gastrointestinal, genitourinary, nervous, and skeletal systems while also noting the quality of pain, radiation, intensity, time of onset, and duration. Relevant surgical interventions include urinary incontinence

TABLE 42.1 Location of Pelvic Pain and its Causes

Location of Pain	Potential Explanations
Vulva	Infection, exposure (irritants), vulvar atrophy (hypoestrogenism), low testosterone, neuropathy, dermatologic conditions (Lichen Sclerosis)
Introitus	Low testosterone, friction (from clothing or sexual activity), irritant (spermicide)
Urethra	Vulvovaginal atrophy, friction, tight external sphincter muscle or stricture, tumor, infection, diverticulum
Pelvic floor muscles	Dysfunctional voiding, muscle overactivity
Bladder	Interstitial cystitis, bladder outlet obstruction
Anorectum	Constipation, fissures, hemorrhoids, levator ani syndrome/proctalgia fugax, hernia
Localized pain	More likely to be organ-based or in a nerve distribution
Widespread pain	Central sensitization, small fiber polyneuropathy, rheumatologic disease, fibromyalgia, association with anxiety, personality disorders, history of sexual abuse

Adapted from *Facing Pelvic Pain*.[5]

TABLE 42.2 Organ System Contributors to Pelvic Pain

Organ System	Potential Explanations
Gynecologic	Endometriosis, endometritis, uterine fibroids, ovarian pathologies, sexually transmitted infection (STI), pelvic inflammatory disease, tumor
Male genital	Prostatitis, epididymitis, testicular pathologies, ejaculatory duct or vas deferens obstruction, STI
Urologic	Interstitial cystitis, stone (distal ureter or bladder), tumor, urinary tract infection or STI, urethral caruncle, stricture
Gastrointestinal	Irritable bowl syndrome, chronic proctalgia, levator ani syndrome, constipation, fissures, hemorrhoids, anal cancer, warts, tumor, diverticulitis, appendicitis, adhesions, inflammatory bowel disease
Musculoskeletal	High tone pelvic floor muscles, back, knee, foot, or hip problem, myopathy, osteitis or osteomyelitis, injury to bones, ligaments, or tendons
Neurologic	Upper and lower motor neuron syndromes, peripheral neuropathies, spinal disc disease, tethered cord, sacral tumor, entrapped peripheral nerve
Psychological-associated conditions	Central sensitization, depression, anxiety, sexual abuse, personality disorders, couple distress, grief over lost function
Vascular	Pelvic venous congestion, vasculitis

Adapted from *Facing Pelvic Pain*.[5]

surgery, prolapse surgery, hysterectomy/oophorectomy, abdominal incisions, bowel or hernia surgery, and spinal surgery. A clear chronology referable to surgery raises suspicion of nerve entrapment. Assessment of previous treatments and whether they have been successful is of vital importance, as this can guide future management.

When conducting the physical exam, a good neurologic exam is essential, including dermatomes associated with the pain and observance of gait. The pelvic exam is easiest to introduce by applying the concept of trauma informed care, for example, "it would be helpful to do an internal exam of the pelvic area, and if you agree we have time to do it today. Is there anything about your comfort with the exam that you would like us to know?" This type of introduction puts the patient in control, as many patients can feel overwhelmed by such an examination.[15]

Laboratory and imaging studies will be ordered based on the diagnostic suspicion. Urinalysis and culture, urine cytology, stool tests, and completion of a voiding diary are easily obtained. With the advent of polymerase chain reaction (PCR) for sexually transmitted infections (STIs), screening can be performed on the urine or a simple vaginal swab without the need for complicated specimen acquisition or how to read a wet prep. Diagnostic studies such as endoscopy, pelvic and abdominal ultrasound or computed tomography (CT) scan, and MRI of the spine, head, abdomen, and pelvis can also help in diagnosis.

Pelvic Pain That Should Not Be Missed: Dangerous Acute Causes and Cancer

The pain management specialist should not often be in the position of evaluating acute pelvic pain or diagnosing cancer; patients typically will have had an evaluation, exam, and imaging by a pelvic floor specialist prior to referral. Given that the pain specialist may have ethical or liability concerns regarding missed diagnoses, acute pain and cancer will be briefly reviewed below.

Acute pelvic pain is defined as the presence of pelvic pain for less than three months' duration but is typically thought of as sudden onset and requiring immediate evaluation.[16,17] The physician will need to rule out etiologies that are potentially life threatening in the setting of the sudden appearance of pain. About 10% of all emergency department (ED) visits correspond to the development of abdominal pain, with some sources citing figures as high as 21%–34%.[17,18] The exact prevalence of pelvic pain in the ED is difficult to estimate, as symptoms are often associated with those of lower abdominal pain.

The initial evaluation of acute pelvic pain should include vital signs, temperature, assessment of symptoms such as fever, chills, discharge, or vomiting, and previous diagnoses (e.g. STIs) and risk factors. A broad differential should be considered, given the number of organ systems contained within the pelvis.[16] Pregnancy status should be assessed if there is any potential via b-hCG (either blood or urine testing) or ultrasound, as it can be used to determine the presence of a gestational sac or free fluid within the abdominal cavity.

The most common causes of acute pelvic pain are gynecologic (e.g. ovarian torsion or cyst, ectopic pregnancy, PID, endometriosis) and gastrointestinal conditions (e.g. appendicitis, diverticulitis, hernia, SBO), followed by urinary tract etiologies (e.g. urinary tract infection [UTI], cystitis, ureterolithiasis).[16,17] The initial approach should rule these out. A low threshold should be maintained for pregnancy tests, urinalysis and culture, serology, imaging, referral to other specialties, and ED evaluation. Table 42.3 summarizes the acute causes of pelvic pain by the organ system.

TABLE 42.3 Acute Causes of Pelvic Pain by Organ System

Organ System	Potential Explanation
Gastrointestinal	Appendicitis, hernia, diverticulitis, small bowel obstruction, adhesions, functional abdominal pain
Gynecologic	Ectopic pregnancy, pelvic inflammatory disease, ovarian torsion, ovarian cyst, ruptured ovarian cyst, endometriosis, malpositioned intrauterine device, toxic shock syndrome, sexually transmitted infection, tubo-ovarian abscess
Male Reproductive System	Testicular torsion, epididymitis, prostatitis
Urologic	Pyelonephritis, ureterolithiasis, urethritis, cystitis
Musculoskeletal	Fractured pelvic bones, enthesitis, seronegative arthritis
Neurologic	Cauda equina syndrome

Cancer is a potential cause of pelvic pain, manifesting with a range of presentations, as it can damage any structure or nerve. Typically, the pain specialist will be collaborating with pelvic specialists who will take responsibility for this part of the differential diagnosis. Somatic pain occurs when cancer extends through the fascial planes and stimulates the nociceptors in supporting structures. Neuropathic pain can occur with direct extension to the pudendal and perineal nerves or lumbosacral plexus. Visceral pain arises when the tumor causes spasms of smooth muscles in hollow organs and distorts the capsule of solid organs. Traction on adjacent organs, ischemia, and inflammation also incur pain. The most common cancers to rule out in this setting are gynecologic cancers (e.g. cervical, uterine, and vaginal cancers) and malignancy within the colon, rectum, prostate, and penis.[19] Blood in the urine, stool, or ejaculate, or vaginal or urethral bleeding should warrant referral for evaluation. In addition, a good rule of thumb is that pelvic pain refractory to the initial evaluation and management warrants imaging and specialty referral.

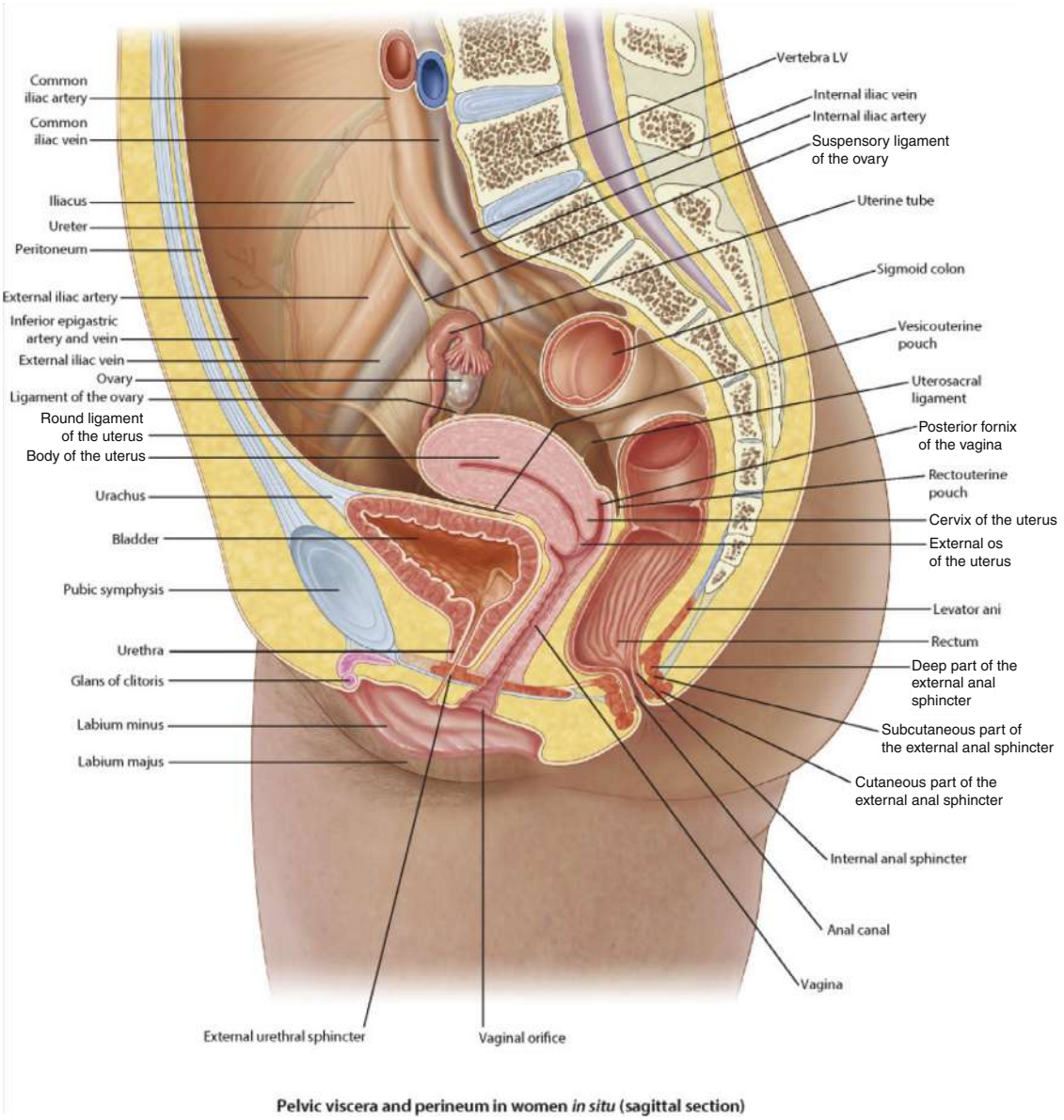
Organ-Based Causes of Pelvic Pain With Treatment

Gynecologic Considerations

This section will discuss acute and chronic gynecologic causes of pelvic pain, referring to pelvic pain stemming from anatomically female internal and external genitalia. Patients born with ambiguous genitalia or who have undergone gender affirmation surgery may benefit from both this and the next section on male anatomy. Fig. 42.1 details the female pelvic anatomy.

Evaluation of female pelvic pain includes a thorough obstetric, gynecologic, surgical, psychiatric, and medical history; and musculoskeletal, abdominal, and pelvic exam. Imaging may include ultrasound and MRI, and laboratory tests may include hormones, vaginal evaluation for infectious organisms, and tumor and inflammatory markers.[20]

Common gynecologic causes of acute pelvic pain include ectopic pregnancy, ovarian cyst rupture, Mittelschmerz (a milder form of ovarian cyst rupture, which is a natural part of ovulation), ovarian or fallopian tube torsion, PID, tubo-ovarian abscess, fibroid degeneration or torsion, and endometriosis. When evaluating acute causes of gynecologic pelvic pain, conditions such as UTI,



• **Figure 42.1** Female pelvic anatomy. From: Drake RL, Vogl A, Mitchell WA. Pelvic viscera and perineum in a female *in situ* (sagittal section). In: *Gray's Atlas of Anatomy*. 3rd ed. Philadelphia, PA: Elsevier; 2021:213–292.

kidney stones, appendicitis, diverticulitis, bowel obstruction, volvulus, intussusception, or bowel ischemia must be considered.

In acute gynecologic pelvic pain, the priority should be on determining if emergent care is needed or if the condition can be managed in an outpatient setting. Emergent treatment, including potential surgery, is necessary for conditions related to intra-abdominal hemorrhage, organ infection, or acute ischemia (e.g. torsion). Pain refractory to over-the-counter medications, fever, nausea, and vomiting, inability to ambulate, fainting, or orthostasis should prompt emergent care referral. The two most concerning acute gynecologic conditions are ectopic pregnancy and adnexal torsion. Appendicitis and diverticulitis need to be considered as well. If a patient has a positive pregnancy test coupled with pelvic pain, with or without vaginal bleeding, pelvic ultrasound should be performed, and obstetric referral for ectopic pregnancy should be prioritized as soon as possible. If diagnosed, surgery is indicated in the setting of a ruptured fallopian tube; methotrexate administration may be an option to preserve an intact fallopian tube if the patient is stable. Neither treatment will salvage the pregnancy. In the case of ruptured ovarian cyst, it is often sufficient for physicians to monitor for signs of infection and bleeding and to trend complete blood counts while managing pain. Surgery is required if the hemoglobin drops significantly or if the ovary or fallopian tube is twisted/torsed and therefore ischemic. Expedient diagnosis (typically via duplex doppler ultrasound) is necessary to salvage the organ. Less emergently, torsed uterine fibroids may require surgery. Endometriosis is more of a chronic pain diagnosis that can exhibit acute manifestations. Evaluation of acute pain should include an abdominal and pelvic exam, pregnancy test, complete blood count with differential, cervical cultures/PCR for sexually transmitted infection, a pelvic ultrasound, and focused assessment sonography for trauma exam as indicated (e.g. to evaluate for the

presence of free fluid within the abdominal cavity). Acute pain management should first be attempted with prescription strength ibuprofen, ketorolac, or other nonsteroid medications before proceeding to narcotics.

CPP is common in females, as mentioned above, affecting 15%. Endometriosis affects about 6%–10% of all females. In endometriosis, tissue similar to the lining of the uterus is found at ectopic locations. This ectopic tissue reacts to cyclic hormones in the same way that the endometrium lining the uterus does, leading to chronic inflammation and scarring. Clinical symptoms suspicious for endometriosis include excessively painful menstruation, painful sexual intercourse, or painful bowel movements. The cyclic pain is the hallmark symptom because of irritating prostaglandin release and bleeding. A physical exam can reveal deposits of endometrial tissue in the vagina or palpable endometrial nodules posterior to the uterus, but often exams and imaging are unrevealing. MRI or pelvic ultrasound may show blood-filled ovarian cysts. Definitive diagnosis may require laparoscopy for direct visualization of organs and biopsy. Treatment of endometriosis includes medical management and surgery. Medications include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen for pain, but hormonal therapy to counteract endometrial growth resulting from estrogen is the mainstay of treatment. Examples include oral contraceptive pills, progesterone-only birth control (including the progesterone-releasing intrauterine device [IUD], contraceptive implants, medroxyprogesterone acetate injections, and norethindrone), and agents impacting gonadotropin-releasing hormone (leuprolide acetate, goserelin, and elagolix). Surgery is utilized to remove or destroy the ectopic tissue through the removal of ovarian cysts and excision or cauterization of ectopic foci, while hormonal medication is often used postoperatively to prevent recurrence.[21–25]

Adenomyosis is an endometriosis variant, occurring when endometrial tissue invades into the myometrium. Adenomyosis causes hypertrophy, hyperplasia, and fibrosis in the uterine wall. Adenomyosis *can* cause severe menstrual pain and heavy menses. Adenomyosis causes severe menstrual pain and is less common in nulliparous females. Pain is usually localized to the suprapubic midline and is worse during menstruation but may be present throughout the month. Hysterectomy is the definitive cure, but hormonal medications, particularly progesterone-releasing IUDs, which deliver hormone directly to the area of interest, are first line therapy. The desire for future fertility is a fundamental consideration in management.

Ovarian cysts can manifest as painless, chronically painful, or symptomatic during exercise, sex, or menstruation. Pain that aligns with ovulation (also known as mittelschmerz) occurs because of natural functional cysts that rupture when the egg is released. The pain often alternates sides monthly. Mittelschmerz is relieved by medications that stop ovulation, such as oral contraceptives, progesterone implants, or medroxyprogesterone acetate injections. A complete evaluation by a gynecologist is necessary to rule out cancerous cysts, but benign cysts are much more common. Benign ovarian tumors may lead to chronic one-sided pain that does not become acutely painful unless ovarian torsion or rupture is involved. The most common type of benign cyst is a dermoid or mature teratoma, including hair, fatty fluid, cartilage, or teeth; other benign cysts include serous or mucinous adenomas. Evaluation of cysts begins with ultrasound, and if they are symptomatic and causing pain that affects the patient's life to an unmanageable degree, laparoscopic ovarian cystectomy can be performed. If the cyst is small and painless without concerning imaging features, it can be monitored with ultrasound.

Over 50% of females have uterine fibroids by the time they are in their 40s. They are usually painless unless they are located at the lining of the uterus and cause heavy menstruation, or they become large enough to outgrow their blood supply and begin to degenerate. Treatment of submucosal fibroids involves removal via hysteroscopy, while intramural or subserosal fibroids can be removed through an abdominal approach.

PID stems from infections of the uterus, fallopian tubes, and ovaries. PID often originates from bacteria that enter the uterus through the vagina, such as those from STIs, but can also arise from vaginal or gastrointestinal tract bacteria. The time course from onset may vary, but PID can lead to chronic pain that may stem from low grade infection or residual scar tissue. Standard evaluation of females with CPP includes sexually transmitted disease testing.

Pelvic organ prolapse is sometimes a cause of female pelvic pain. Prolapse is caused by vaginal wall relaxation/herniation and laxity of the fascial supports, leading to protrusion of bladder, bowel, or the uterus toward the vaginal opening. Pain is typically present in the upright position and worsens as the day goes on. Patients often, but not always, appreciate a vaginal bulge. Diagnosis is based on pelvic exam, and treatment includes observation, pelvic floor physical therapy, pessary, or surgery. Pelvic floor myofascial dysfunction and pelvic venous disorders discussed below can mimic a feeling of pelvic organ prolapse.

Vaginal pain may be caused by vaginal atrophy, myofascial pain, inflammation/infection, or pain disorders such as endometriosis or painful bladder syndrome. More rarely, a vaginal septum, a Gartner's duct cyst (remnant of the mesonephric duct), a chronically inflamed appendix, or scarring from prior surgery can cause pain. Complete evaluation involves a speculum exam, vaginal swabs or cultures if indicated, and an internal digital exam of the levators, bladder, and rectum through the vaginal wall. Treatment options include topical creams or suppositories, pelvic floor physical therapy, transvaginal trigger point injections, or treatment of the aforementioned underlying conditions. If pain with sexual activity is involved, a professional sexual health therapist may be beneficial.

Causes of vulvar pain may involve vaginal atrophy, chronic infections, inflammatory skin conditions, scarring from childbirth, or neurologic cause (such as vulvodynia or neuropathy). Diagnostic workup includes an external vulvar Q-tip exam (targeting the Skene's glands at 11 and 1 o'clock and the vestibular glands at 5 and 7 o'clock) and internal vaginal exam, often cultures, and potentially a biopsy. Treatment can include topical ointments, oral medications, and physical therapy. Vulvovaginal atrophy can cause burning or UTI, which can be treated with topical estrogen cream. Surgery is only rarely indicated in vulvar pain. One successful intervention is the simple avoidance of irritants such as filamentous paper products, perfumes, spermicides, and harsh cleansers.

Gynecologic cancer is a rare cause of pelvic pain. Ovarian cancer may involve abdominal bloating, distention, or a vague diffuse pelvic pain. Other symptoms include increased urinary frequency, constipation, or anorexia. Diagnostic evaluation for malignancy includes pap smears, internal and external pelvic exam, pelvic ultrasound, and biopsy of suspicious tissue. Imaging is indicated in refractory pelvic pain.

Pain related to sexual activity may need to be specifically raised by the interviewer. It may occur during or after penetrative sex, arousal, or orgasm and can be very disruptive to a relationship. Pain with sexual activity can affect individuals at any age, of all sexual orientations and sex. Diagnosis and evaluation of pelvic pain stemming from sexual activity requires an external and

internal pelvic exam to include the pelvic floor muscles and may necessitate additional testing such as complete blood count (CBC) (e.g. to evaluate for the presence of occult bleeding), chemistry testing, thyroid function test, urinalysis with reflex to urine culture, luteinizing hormone, follicle-stimulating hormone, estradiol (E2) or imaging (likely ultrasound). The most common gynecologic causes of sexual pain are genitourinary syndrome of menopause, infection, endometriosis, and benign gynecologic tumors, but high tone myofascial dysfunction is the most common cause of pain with penetration. Treatments, such as lifestyle modifications, physiotherapy, pharmacotherapies, psychosocial treatments (including a certified sex therapist), or surgery, should be utilized appropriately depending on the underlying causes identified.[26]

An important but rare entity to be aware of is persistent genital arousal disorder. Females complain of unwanted clitoral sensation ranging from engorgement to arousal to pain. Etiology can be local (a foreign body under the prepuce), neurologic (small fiber polyneuropathy or radiculopathy, Tarlov cysts), medication-related, or vascular (arteriovenous formation).

Treatment for CPP is best achieved using a multimodal approach involving non-pharmacologic treatments and medications. The goal should be to tailor treatment as much as possible to the underlying causes. More than 50% of females with CPP will have no clear inciting cause identified, so more global approaches can be just as important. Non-pharmacologic therapies include pelvic floor physical therapy, psychotherapy, acupuncture, and neuromodulation. Pharmacologic interventions include non-opioid analgesics, hormonal modulation, membrane stabilizers, antidepressants, and in rare cases, opioids.[27]

Male Urologic Problems (Including Sexual Pain)

This section will discuss pelvic pain related to male anatomy, including the prostate, epididymis, seminal vesicles, testis, and penis. Myofascial dysfunction of the pelvic floor, discussed below, commonly affects males as well. Fig. 42.2 details de male pelvic anatomy.

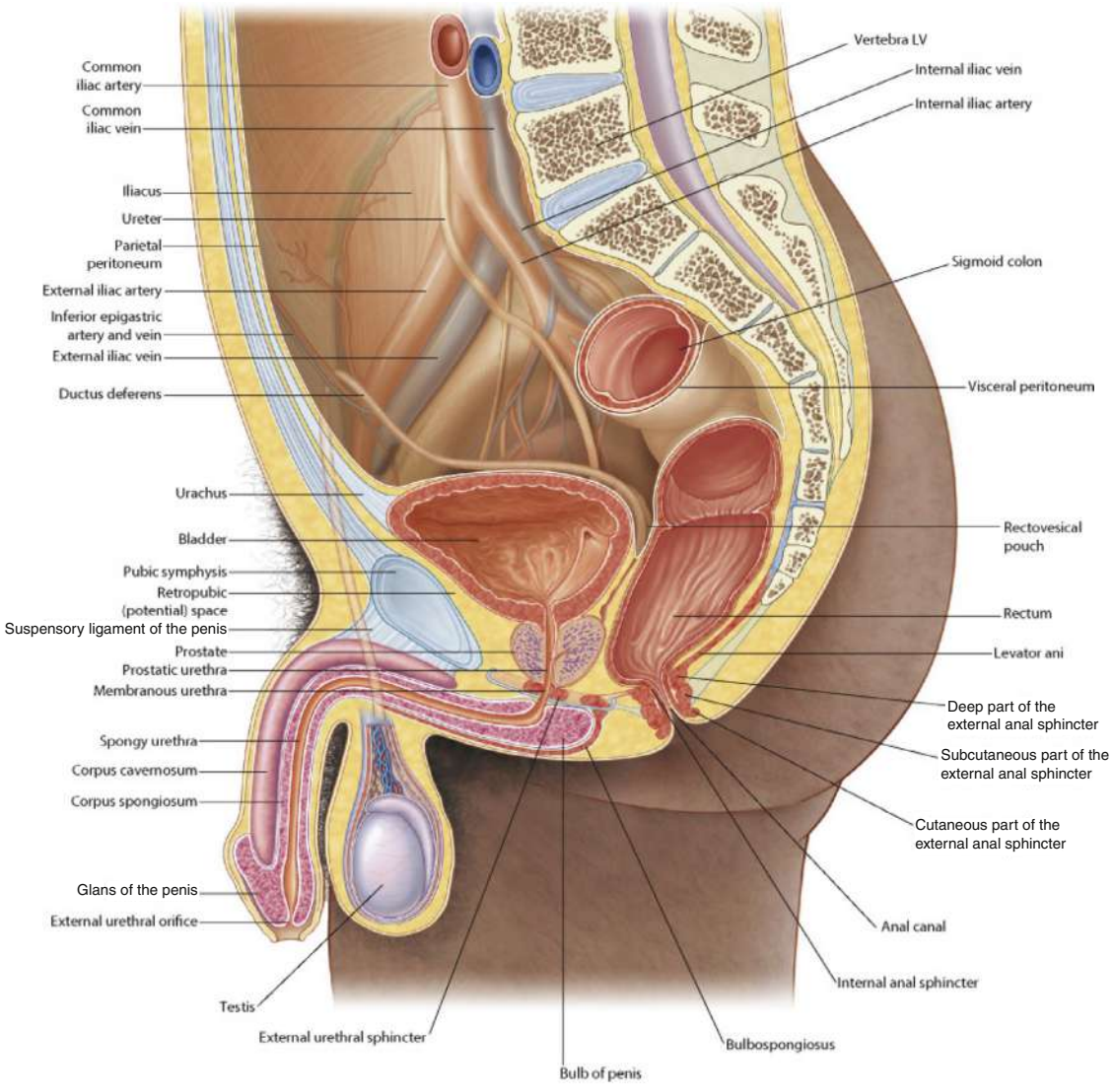
Several conditions related to the prostate may result in pelvic pain, including benign prostatic hyperplasia, acute prostatitis, and prostate pain syndrome (PPS).[28] As males age, the prostate can increase in size. The tone of the smooth muscle within the prostate and bladder neck is important and, if high, can cause a weak urinary stream, urinary urgency or frequency, or incomplete bladder emptying. Bladder outlet obstruction may lead to pain as the bladder strains and becomes relatively ischemic during urination or if residual volume is increased. Treatment will include α-blocker medications, which relax the smooth muscle of the bladder neck, and prostate, and potentially pelvic floor muscle physical therapy. *Acute prostatitis* is caused by bacterial infection of the urinary tract and prostate; this leads to pain in the pelvis, lower abdomen, testicles, penis, and urethra or during actions such as urination or ejaculation. Symptoms can include fever, nausea, and vomiting and require emergent medical attention. Diagnosis is by urinalysis and culture, physical exam showing a tender boggy prostate (however, as the exam can lead to sepsis, it is avoided where possible), and imaging (ultrasound, CT scan, or MRI). PPS, previously called chronic prostatitis, has symptoms similar to acute prostatitis, but there is often no evidence of infection. Treatment in this case would not include antibiotics but rather pelvic floor physical therapy and muscle relaxant or anti-inflammatory medications. Evaluation of prostatic causes of pelvic pain includes urine culture, digital rectal exam to include the pelvic floor muscles, measurement of post-void residual urine assessment, potentially cystoscopy or urodynamic testing, and imaging studies such as ultrasound, CT, or MRI. Surgery may be beneficial, especially if an obstruction is present or if prostate stones are identified and thought to be harboring bacteria (30%–70% success).

Management of chronic pain in the epididymis, seminal vesicles, testes, and penis can include physical therapy, anti-inflammatories, neuromodulators, acupuncture, and nerve blocks. These paragraphs will address more specific causes and treatments, best managed with a urologist subspecialized in infertility and men's sexual health. Pain in the epididymitis may be acute or chronic. Acute epididymal pain is likely because of infection and necessitates urgent medical evaluation. In younger males, it is more typically because of STIs such as *C. trachomatis*; in older males, epididymis is more likely to be from gastrointestinal bacteria such as lactose positive colibacillus. Viral epididymitis is also possible, more so in children. Symptoms include pain and swelling of the epididymis and scrotum, urethral pain and burning during urination, pain above the pubic bone, and occasionally fever, chills, and flank discomfort. Diagnosis is based on urine PCR for STI, urine culture for UTI, and scrotal ultrasound. Treatment includes scrotal elevation, pain control, and antibiotics. Pain often takes up to six weeks to dissipate after treatment initiation (an important counseling point); it is imperative to treat such conditions immediately as complications include abscess formation, secondary infertility, and (rarely) testes infarction. Chronic epididymal and vas deferens pain may be associated with cysts, but often the workup is non-specific. Management varies depending on clinical exam and symptoms (for example, identification of an associated varicocele).

The seminal vesicles and ejaculatory ducts are rarely causes of pain, with congenital anomalies being the most likely cause (e.g. ejaculatory duct cyst). Rarer causes of chronic infections such as tuberculosis or schistosomiasis may occur. The primary symptoms are usually pain with ejaculation or low ejaculate volume, and evaluation entails a physical exam, urine culture, and transrectal ultrasound or pelvic MRI. Treatment is based on the underlying anatomic finding, such as an ejaculatory duct stone.

Testicular pain can also be separated into acute and chronic causes. Acute testicular pain is a medical emergency as it can be because of testicular torsion. Other essential diagnoses include testis fracture, a palpable mass that may point to malignancy or orchitis. Chronic causes of testicular pain should be evaluated by physical exam (intermittent torsion secondary to bell clapper deformity) and scrotal ultrasound with attention to blood flow, mass, or abscess. Chronic pain may be treated empirically with a trial of antibiotics or anti-inflammatory medication if the cause is unclear. Potential causes include nerve hypersensitivity, especially in the setting of systemic neuropathy or a prior surgical procedure. Suppose conservative treatment, including pelvic physical therapy and gabapentinoids, fails. In that case, one can try an anesthetic nerve block, targeted denervation of the spermatic cord, targeted peri-spermatic cord cryoablation, an off-label botulinum toxin injection, and potentially a more generalized nerve block.

Pain in the penis can stem from infectious or non-infectious origins. Symptoms of infection include urethral discharge, ulcerations, blood in the urine, or referred pain from the urethra. An acute penile fracture is often accompanied by a sudden "popping" and is diagnosed via ultrasound or MRI; it requires urgent surgery. More chronic pain during intercourse may be connected to Peyronie's disease, prostatitis, or inflammation of the seminal vesicles.



Pelvic viscera and perineum in men *in situ* (sagittal section)

• **Figure 42.2** Male pelvic anatomy. From: Drake RL, Vogl A, Mitchell WA. Pelvic viscera and perineum in a male *in situ*. In: *Gray's Atlas of Anatomy.* Philadelphia, PA: Elsevier; 2021:213–292.

Peyronie's disease is diagnosed by a history of an angled erection and via physical exam revealing an induration of the penile shaft (tunica albuginea). This may be visible as a plaque on penile ultrasound. Peyronie's disease does not always require treatment, but injecting collagenase clostridium histolyticum into the scar tissue may relieve pain. Surgery is used to correct severe curvature to restore sexual activity but is not a targeted treatment for pain.

It should be remembered that systemic neuropathy, rheumatologic, vascular, and myofascial disorders can contribute to the above sources of seemingly sex- or organ-based pain.

Urogenital Etiology of Pain

This section will discuss pelvic pain related to the bladder, urethra, and ureter. Urethral pain is usually related to voiding and can be accompanied by dull pressure that radiates to the groin, sacrum, or perineum. Urethritis is typically caused by a UTI. Diagnosis is based on a voided urine test with a culture of over 100,000 colonies of one bacteria strain and over ten white blood cells from the urine sediment or on a catheterized specimen with over 10,000 colonies of bacteria. Urethritis that is not from a UTI is commonly caused by STIs. Physical exam may show STI-specific findings, including rashes, but typically evaluation is by screening with a vaginal swab in females and urine or urethral discharge analysis in males, sent for broad PCR amplification and analysis. The most common STIs are chlamydia and gonococcus; rarer organisms include urea plasma and mycoplasma genitalium. Treatment for both urinary tract infections and STIs is provided with appropriate antibiotics and, if necessary, behavior change. A rarer cause of urethral pain is a urethral diverticulum. Urethral diverticula are benign epithelium-lined outpouchings of the urethra, which are much more common in females than males.[29] Many people

are asymptomatic, but signs and symptoms may include CPP, post-void dribbling, urinary obstruction, stress urinary incontinence, intermittent passage of pus or blood in the urine, recurrent UTI, painful vaginal mass, and pain during vaginal penetration. The most sensitive diagnostic tool is MRI, but suspicious physical exam findings include a palpable mass. Mechanical pressure on the urethra can cause milky urethral fluid to elicit via the meatus. Cystoscopy may show an ostium (opening) in the urethral lumen. A Skene's duct cyst can cause urethral pain in females but does not connect to the urethra and is found at the distal urethra. Other urethral causes of pain specific to females are urethral caruncle and urethral mucosal prolapse, occurring almost exclusively in the setting of vaginal atrophy. Urethral caruncle is a benign growth of the posterior urethra, and urethral mucosal prolapse is a loosening and slippage of the mucosal lining of the urethra. Most commonly, there are no symptoms, but some females have blood in the urine, vaginal bleeding, or severe pain with a large edematous inflammation of the lesion. In asymptomatic cases, treatment is not needed. Estrogen cream is the first line treatment if symptoms occur and there is no contraindication (e.g. breast cancer). If the caruncle or mucosal prolapse does not respond to treatment, is large, changes in size or appearance, or has an unusual appearance, further evaluation with cystoscopy or biopsy may be warranted to rule out malignancy. Urethral pain in males and females can also occur because of nerve sensitivity, such as small fiber polyneuropathy or nerve entrapment (pudendal and/or genitofemoral nerve). Chemical irritants, food sensitivities, or vaginal atrophy can affect the nerves of the urethra.

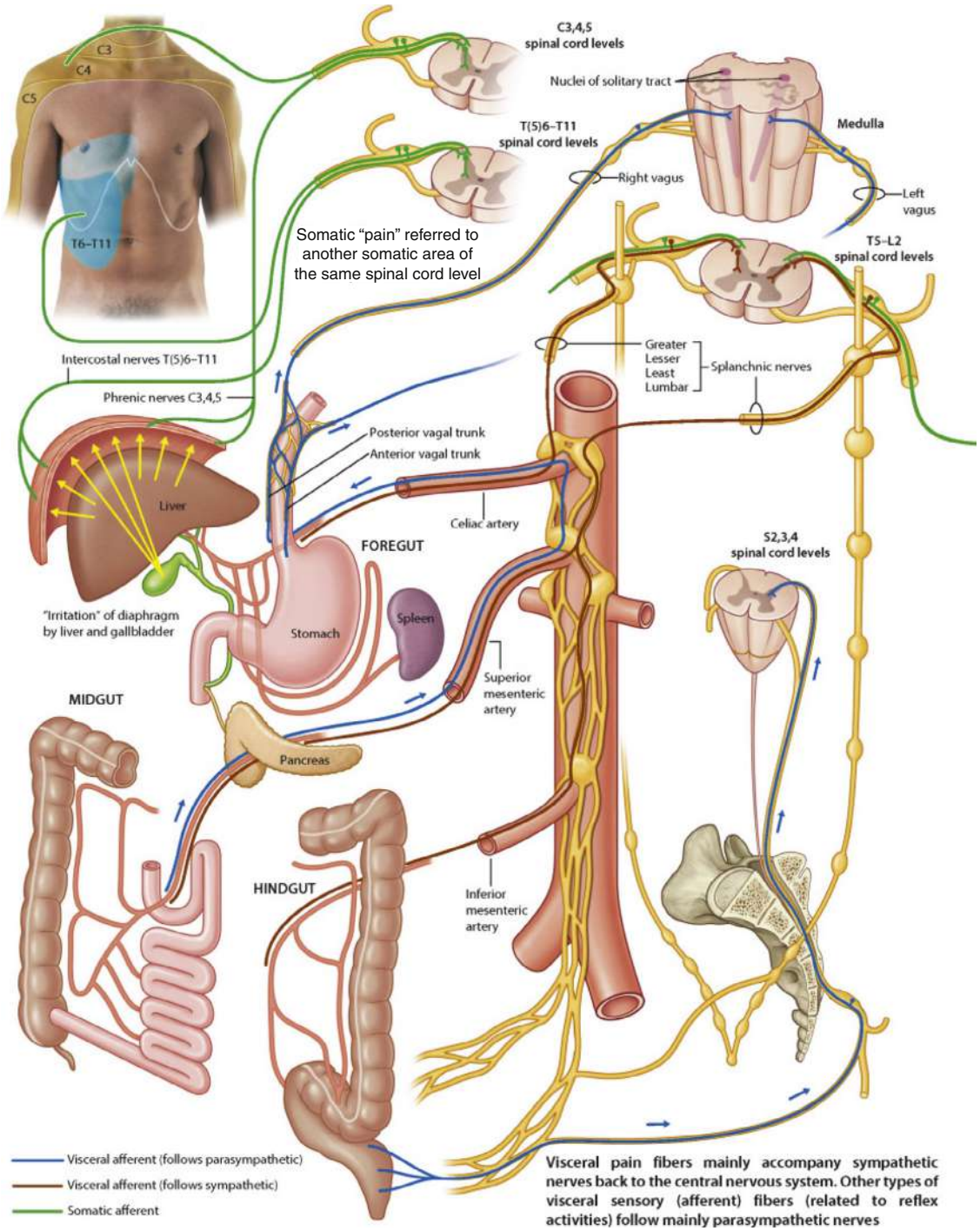
There are several bladder related conditions that can lead to pelvic pain. Interstitial cystitis or bladder pain syndrome is a diagnosis of exclusion and is defined as "(…) an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks' duration, in the absence of infection or other identifiable causes."[30] Pain is often exacerbated by specific food or beverages and improves with voiding. It may radiate to the urethra, vulva, vagina, rectum, lower back, or abdomen. Evaluation includes a thorough history, physical exam, voiding diary, urine testing, and potentially cystoscopy. Treatment begins with habit modification, then physical therapy and medications, hydrodistension, off-label botulinum toxin injection, off-label sacral neuromodulation. Treatment can progress to medications such as immune-based cyclosporine A and (rarely) extirpative surgery. Another potential bladder source of pelvic pain is overactive bladder (OAB), a syndrome characterized by urinary urgency with daytime frequency, nocturia, and urgency urinary incontinence. Diagnosis is via physical exam, history, questionnaires, urine analysis, and post-void residual bladder scan. Treatment begins with dietary irritant modification, pelvic physical therapy, and bladder training. It then progresses to anticholinergic and β3 agonist medications. Treatment may include on-label sacral neuromodulation or botulinum toxin injection to the detrusor muscle. Bladder outlet obstruction is characterized as either functional or anatomic. Anatomic obstruction in females is typically because of anterior vaginal wall prolapse (cystocele), urethral diverticulum, or complications from a previous intervention such as a sling. In males, obstruction can occur because of an enlarged or tightened prostate or in both sexes from a urethral stricture. All these causes are treated surgically. Functional obstruction accounts for most bladder outlet obstruction in females and is diagnosed via video urodynamic studies.[31] It is typically caused by increased tone or failure of relaxation of the bladder neck. High tone in the external urethral sphincter can be seen in the setting of pelvic floor muscle dysfunction. Neurologically mediated obstruction is often the first sign of multiple sclerosis and is caused by dyssynergia of either the internal (bladder neck) or external urethral sphincter. Treatment of female bladder outlet obstruction begins with pelvic floor physical therapy, α-blockers, intermittent self-catheterization, and off-label injection of botulinum toxin. If neurologic disease is suspected, a referral is made concurrent with intervention, and physical therapy may be less likely to succeed. Underactive bladder can cause pelvic pain because of high post-void urine residual volumes. It is characterized by prolonged urination time, possible feeling of incomplete emptying, urinary hesitancy, weak stream, and straining when urinating. It is diagnosed via post-void residual measurement and urodynamic testing and may require cystoscopy to exclude other etiologies. Treatments include behavior modification, pelvic floor physiotherapy, α-blocker medication, and intermittent or indwelling catheterization. Further treatment steps may include indwelling suprapubic catheter or diversion of urine; in idiopathic (non-neurogenic) retention, sacral neuromodulation may be successful.

CPP arising from the ureters is rare but can most certainly occur in the setting of a missed distal ureteral stone. Clues would include sudden onset of pain and urinary symptoms with occasional flank pain. Obstruction of the ureter can occur because of endometriosis or surgical scarring, or because of a congenital abnormality (ureterocele). Diagnosis would be via ultrasound, MRI, or CT scan, and treatment includes NSAIDs, α-blocker medications, and surgical management of any anatomic lesions. Hyperalgesia can persist in the ureters after stone passage.[32]

Malignancy of the urinary tract should be investigated if gross hematuria is present; this should neither be confused with dietary or synthetic changes to urine color (e.g. beets) nor ignored because of the use of anticoagulation. Microscopic hematuria is defined as ≥3 red blood cells per high power field in the absence of infection. Hematuria obligates renal mass protocol kidney imaging and cystoscopy with a urologist.[33]

Gastrointestinal Problems, Anal, and Defecatory Pain

Several gastrointestinal disorders may contribute to pelvic pain because of the complex visceral innervation of the abdomen (Fig. 42.3). Anorectal causes of pelvic pain can include prolapsed hemorrhoids, anal fissures, abscess, prolapsed rectum, proctalgia fugax, and anal cancer. Gastrointestinal sources may include IBS, inflammatory bowel disease such as ulcerative colitis or Crohn's disease, severe constipation, stricture, obstruction, diverticular disease, or colon cancer. A thorough history of the pain is necessary and should include explicit questions regarding rectal bleeding or black stool, fever, nausea, vomiting, weight loss, swollen joints, skin rashes, severe fatigue, and eye pain. Surgical, medical, gynecologic, and obstetric history may be relevant as well. Signs that point to a gastrointestinal cause of pelvic pain include pain associated with bowel movement, eating, specific foods, and changes in bowel habits. A physical exam should involve visual anal inspection, a digital rectal exam, and potentially an exam with an anoscope. Depending on the initial exam, further investigation may include colonoscopy, MRI, x-ray, defecography, endoanal ultrasound, CT scan, anorectal manometry, or sitzmark study. Below we discuss some specific intestinal and anorectal disorders that cause pelvic pain.



• **Figure 42.3** Visceral innervation of the abdomen. From: Drake RL, Vogl A, Mitchell WA. Gray's Atlas of Anatomy. 3rd ed. Philadelphia, PA: Elsevier; 2021:133–212.

IBS is a functional disorder related to changes in bowel habits that can lead to both chronic abdominal and pelvic pain. Symptoms vary, and diagnosis is often by exclusion. IBS can be associated with traumatic early life experiences, depression, anxiety, and other hypersensitivity disorders such as migraine headaches, chronic fatigue, and fibromyalgia. Various foods can trigger this benign condition, and treatment should begin with diet restriction to exclude dairy, gluten, and fermentable carbohydrates. Treatment may include medications such as gabapentin and low dose anti-depressants, depending on individual patient symptoms. Some patients may be hesitant to discuss symptoms, having been told that it is "all in their head"; thus providers need to explain that there is a biologic cause for IBS symptoms.

Inflammatory bowel disease is commonly split into ulcerative colitis and Crohn's disease. Ulcerative colitis affects the innermost lining of the large intestine, resulting in continuous inflammation that typically begins distally at the rectum and progresses proximally; symptoms include severe (bloody) diarrhea, crampy abdominal pain, fever, weight loss, and fatigue. Evaluation includes colonoscopy to confirm the diagnosis.[34] Crohn's disease

causes "skip-lesions" and can affect any segment of the gastrointestinal tract from the mouth to the anus discontinuously, often with rectal sparing, and involves the entire thickness of the bowel wall. Complications include stricture, abscess, and fistula. Evaluation involves a colonoscopy, CT scan, and blood tests such as fecal calprotectin. Treatment for mild ulcerative colitis may be sufficient with mesalamine, and treatment for severe ulcerative colitis and Crohn's disease can include prednisone and other immune modulators such as azathioprine, remicade, humira, ustekinymba, and vedolizumab.

Refractory constipation can be caused by slow colon transit or pelvic floor dysfunction and other disorders such as colon stricture, rectal inflammation, neurologic disorders, or colon cancer. Evaluation includes a thorough history, colonoscopy, anorectal manometry, sitzmark test, functional testing, or imaging as indicated. Patients may not know they are constipated. Treatment is based on the cause and may include pelvic floor physical therapy, dietary changes, or laxatives.

Previous abdominal surgery can lead to adhesions, which can cause changes in bowel movements or irritation of the peritoneum and is diagnosed via laparoscopy.

Hernias occur when abdominal organs or tissues protrude from a weakening in the peritoneum, with femoral or inguinal hernias most commonly associated with pelvic pain. Inguinal hernias are more common in males and femoral hernias are more common in females. Reducible or painless hernias do not always require intervention, but urgent surgery is necessary if hernias become incarcerated or strangulated. Symptoms of hernia requiring emergent surgery include sudden onset pain, a red or purple bulge, loss of bowel movements, fever, and vomiting.

Hemorrhoids (internal and external) derive from enlarged blood vessels within and surrounding the anal canal. It has been estimated that 75% of individuals will experience hemorrhoids in their lifetime, and the predominant symptom is painless rectal bleeding.[35] Other signs may include anal pain, itching, or discomfort during touching of the anal area. External hemorrhoids typically are asymptomatic unless they become thrombosed, and internal hemorrhoid pain is related to prolapse, strangulation, or thrombosis. Evaluation of hemorrhoids will include a rectal exam, an anoscope exam, and a colonoscopy if other sources of bleeding need to be excluded. Management should prioritize preventing constipation, optimizing positioning during bowel movements, sitz baths, topical preparations, and suppositories that contain hydrocortisone. For hemorrhoids that are not alleviated with conservative therapy, procedures such as banding, cauterization, and sclerotherapy are choices. Surgical options include ligation with or without mucopexy or hemorrhoidectomy.

Irritant dermatitis can occur subacutely from exposure to feces and manifests as skin erosion, erythema, and scaly damage without well-defined borders. Related conditions include overlying fungal (yeast) infection. Older adults are at higher risk of developing irritant dermatitis. Management involves cleaning the skin daily to maintain acidity and keeping the area dry; a skin barrier product containing zinc oxide, petrolatum, or dimethicone should be utilized in cream, lotion, ointment, or liquid form and reapplied after cleaning with every bowel movement. If a fungal or yeast infection is also present, medications such as clotrimazole and miconazole should also be applied. Bulk-forming fiber and products that reduce stool frequency may be useful; avoiding greasy and spicy foods may help stools maintain solidity.

Anal fissures are a tearing of the inner lining of the anal canal either from high anal sphincter tone or from repetitive anal trauma (e.g. chronic constipation). Symptoms include severe pain with bowel movements, minor bleeding, discharge, itching, and burning. Diagnosis can usually be made via history, but gentle physical exam with Q tips may be necessary. Treatment is primarily focused on preventing constipation, while topical agents such as nifedipine or diltiazem (calcium channel blockers) and glyceryl nitrate (GTN) or botulinum toxin injection may also be helpful. If the fissure does not heal with conservative therapy, a fissurectomy or lateral internal sphincterotomy may be required.

Pruritis ani is chronic anal itching leading to perianal skin irritation, pain, and bleeding that can be caused by fecal soiling, contact dermatitis, psoriasis, infection, or certain foods. Diagnosis may require a skin biopsy to exclude Paget disease or malignancy. Addressing the underlying cause is ideal, but barrier creams, maintaining perianal hygiene, and keeping the area dry may help.

Rectal prolapse occurs when there is full-thickness protrusion of the rectum through the anus and is more common in those with weak pelvic floor muscles and rectal fascial attachments or an elongated sigmoid colon. It is more common among females, and risk increases with age. Symptoms include rectal bleeding, mucous discharge, and pelvic discomfort. Usually, the tissue can be mechanically pushed back in; if not, this becomes an urgent issue that requires prompt medical evaluation, as strangulation of the tissue can occur. Evaluation typically necessitates colonoscopy, potentially defecography, and anorectal manometry, and surgery is the ultimate treatment.

Levator ani syndrome involves recurrent dull pelvic or rectal pain lasting for 30 min or more and is often related to levator ani spasm. Treatment can include digital rectal massage, physical therapy, sitz baths, heat or ice, albuterol inhaler, muscle relaxants, botulinum toxin injection, gabapentin, and pain blocks. Proctalgia fugax is a related disorder, with pain lasting up to 30 min and is often more minor, with most patients experiencing fewer than five episodes per year. This pain is thought to be caused by abnormal smooth muscle contraction of the anal sphincter complex. Treatment primarily involves supportive care and topical agents such as diltiazem and glycerol nitrate or inhaled salbutamol.

Musculoskeletal Etiology of Pelvic Pain

Musculoskeletal factors are often overlooked when undertaking a CPP evaluation.[36] However, they have been estimated to have a prevalence ranging from 8%–22% in the United States.[37,38] Taking these numbers into account, it is important to keep musculoskeletal cause high in the differential when evaluating CPP. The patient history should consider previous lower extremity fractures, foot (bunion), ankle, or knee pain, scoliosis, change in ergonomics, or chronic sitting or lifting (e.g. carrying a work bag or young child on one side). Disorders that affect the pelvic girdle or pelvic floor muscles are involved in the development of vaginismus, vulvodynia, proctalgia fugax, and dyspareunia and can even cause entrapment of the nerves (i.e. pudendal neuralgia).[5,39] Pain in the lower back, hips, abdominal muscles, bladder, or bowel may refer pain to the pelvic region. Other common causes of referred pain include damage to the ilioinguinal or hypogastric nerves of the abdominal wall by prior surgery. Alleviating pain from the primary region will typically improve pelvic pain.

Pelvic floor muscles (PFMs) support the pelvic organs, pelvis, and spine, assist with posture, and allow for normal bladder and bowel function in all sexes. Pathologic strain in the PFMs arises from trauma, repetitive use or underuse, or inherent muscle disease, while the pain itself arises from the resulting muscle spasm,

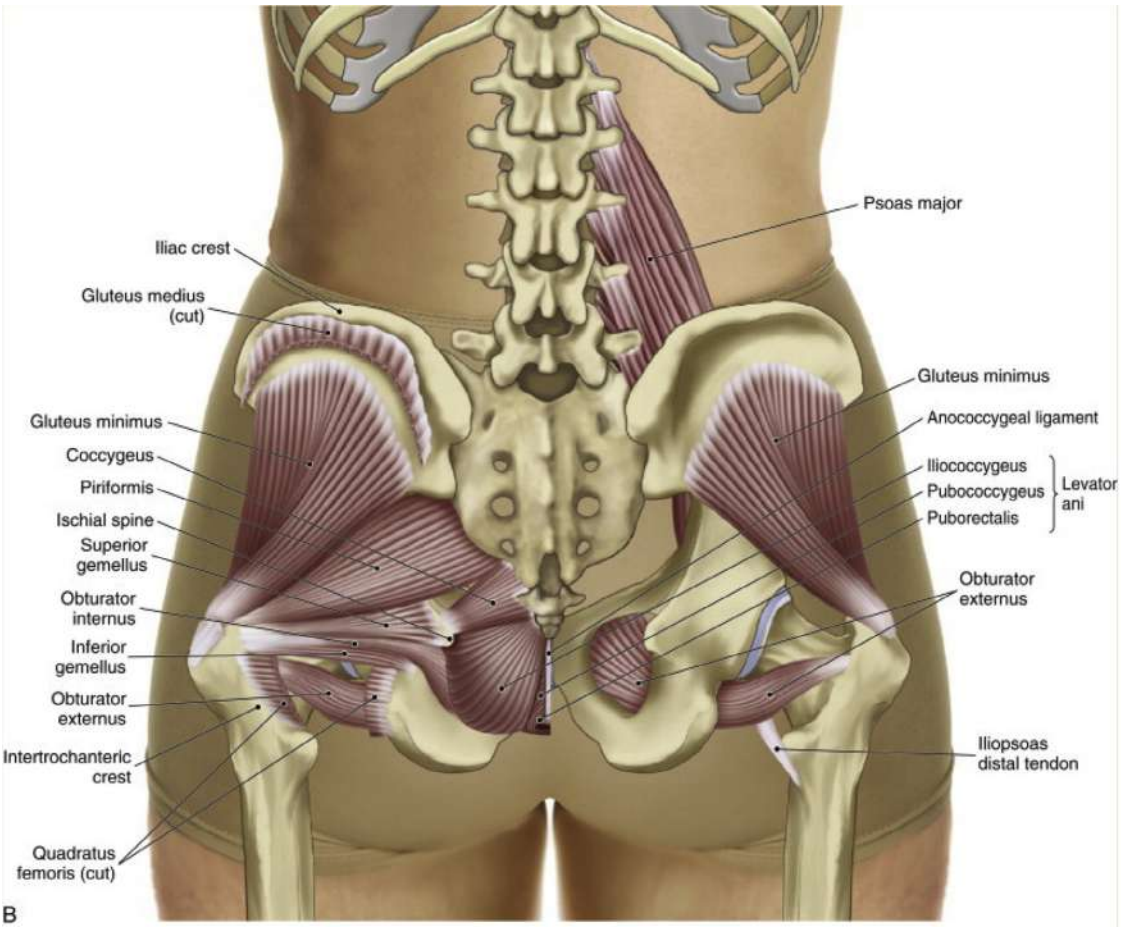
overactivity, or increased muscle tension.[5,40] Hypertonicity of the PFMs is a common cause or contributor to pelvic pain in males and females. It is present on physical exam in up to 87% of females with CPP and 13% of females on screening physical exam.[41,42] Reaction to pain or the stress of musculoskeletal imbalances is a cause of myofascial pelvic pain. This may be associated with symptoms in other pelvic structures such as the bladder, gastrointestinal tract, hip, and back. Myofascial pain is often coupled with pelvic pressure and pain with intercourse, urination, or bowel movements. Diagnosis is based on physical exam, most notable for tight muscle bands, discomfort with palpation, or distinct trigger points similar to those seen in fibromyalgia on exam of the levator, obturator, coccygeus, and piriformis muscles (Fig. 42.4). Diagnostic imaging is not indicated, but the shortening of the muscles has been demonstrated on MRI. Treatment includes pelvic floor physical therapy, relaxation techniques, and medications such as muscle relaxants or off-label trigger point injections with botulinum toxin, steroids, or local anesthetics. Fig. 42.5A–B illustrates the PFMs.

Pathologies that affect the pelvic girdle can also be involved in the development of CPP. For the pelvis to adequately transfer load, it must be well coordinated with all the neuromuscular and articular systems that surround it.[43] Abnormalities within the bones themselves, joints, tendons, or ligaments can make the load distribution inadequate/ imbalanced and precipitate pelvic pain. Fractures of the pelvic bones can occur secondary to osteoporosis or high energy collisions. Damage to the symphyseal ligaments can also occur, either because of trauma or childbirth, resulting in, for example, pubic symphysis diastasis. These patients can experience pain in the anterior pelvis when walking postpartum, and diagnosis is by radiographic separation of >10–13 mm (FPP).

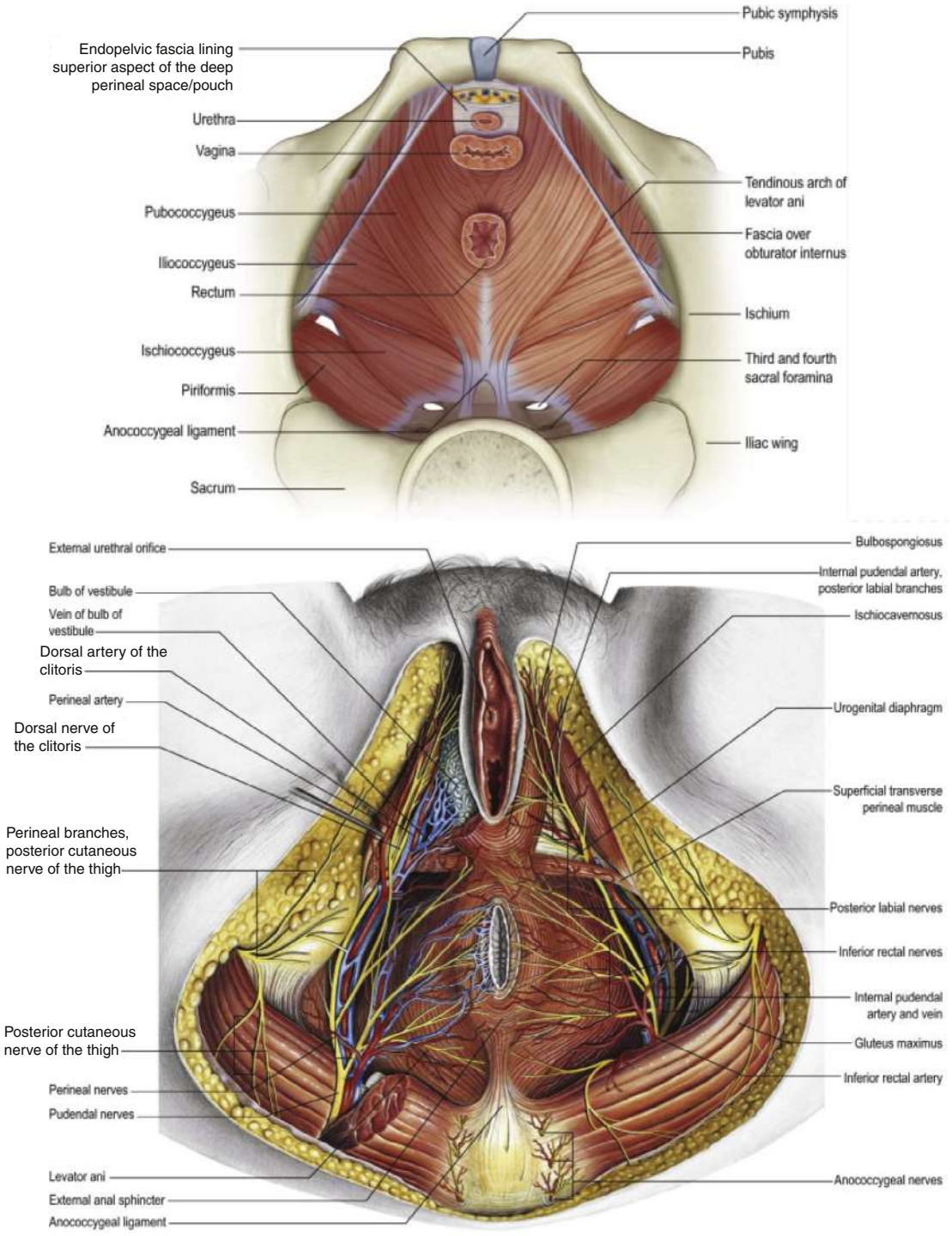
Perhaps unsurprisingly, alterations within structures neighboring the pelvis can also contribute to the development of pain. Dysfunction in the spine or the lower limbs (e.g. scoliosis, flat foot, hamstring tendon rupture) can also impact the transfer of load and have been looked at as potential causes of CPP.[44] The abdominal wall frequently has an impact on pelvic pain, either via radiating/referred pain or by affecting the pelvic girdle mechanics.[45] The hip joints, a common place for arthritis to develop, can also cause CPP via referred pain.[5]

The diagnostic approach should be focused on the history and physical examination (see subsection on H&P) as no single gold standard test exists for the diagnosis of musculoskeletal CPP. Along with the usual questions, history should include any previous history of trauma or symptoms such as pain with defecation, urination, or intercourse. Previous surgical interventions or childbirth instrumentation should also be noted.

For the physical exam, it is important to assess the range of motion, posture, gait, lower limb strength and length, reflexes, and sensory examination. Assessment of internal and external pelvic musculoskeletal structures (e.g. ability to contract or relax, muscle tone, and tenderness) is also of great importance when assessing musculoskeletal causes of CPP. The pelvic floor muscle



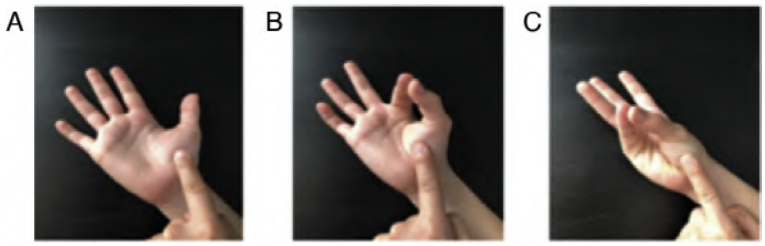
• **Figure 42.4** Posterior view of the coccygeus and levator ani. From Joseph E. Muscolino, The Muscle and Bone Palpation Manual, with Trigger Points, Referral Patterns, and Stretching, 2ed. Elsevier 2016.



• **Figure 42.5** Muscles of the pelvic floor (in a female) including the Levator Ani muscle group, which includes the puborectalis, iliococcygeus, and pubococcygeus muscles. **A,** Top (internal) view with organs, not pictured **B,** Bottom view, including nerves and vessels. (Part A, Reproduced with permission from: Gray's Atlas of Anatomy. The Anatomical Basis of Clinical Practice. 41st Edition. Standring, Susan MBE, PhD, DSc, FKC, Hon FRCS. Elsevier Limited. Published January 1, 2016. Pages 1221-1236.e1. © 2016. Part B, Paulsen, Waschke, Sobotta Atlas of Human Anatomy, 16th Edition 2018 © Elsevier GmbH, Urban & Fischer, Munich)

overactivity (firmness) manual examination is a pragmatic four-point scale of hypertonicity based on comparison of the PFMs to the thenar eminence. Fig. 42.6 illustrates how to quickly assess the tonicity of PFMs.

An asymmetric Trendelenburg gait can be seen with hip dysfunction and myopathies impacting the gluteus medius. Heel or toe walking should raise suspicion of neuropathic weakness. Pain with pubic diastasis will be elicited by bilateral pressure on the trochanters and hip flexion with the legs in extension. Osteitis pubis, which is found typically in young female athletes, leads to painful isometric adductor contraction. The Patrick (FABER: flexion, abduction, external rotation) test can diagnose sacroiliac joint



• **Figure 42.6** The pelvic floor muscle overactivity (firmness) manual examination is a pragmatic four-point scale of hypertonicity based on a comparison of the pelvic floor muscles to the thenar eminence. Normal **(A)**, moderate **(B)**, and severe **(C)** high tone. Hypotonicity would feel softer than the relaxed thenar muscle.

and iliopsoas pain. A positive FABER test suggests sacroiliac joint dysfunction or iliopsoas pain (see Chapter 30).

Some diagnostics that have been of aid in diagnosis in the musculoskeletal cause of pelvic pain include pelvic radiographs, ultrasonography measured sacroiliac joint laxity, and bone mineral density, but in general, unless unstable bony or neurologic lesions are suspected, physical evaluation with a physical therapist certified in pelvic health will be the first (and often only) step.[36]

As with other causes of CPP, multimodal therapy might be needed to achieve the best outcome. Physical therapy techniques are the most important. Musculoskeletal pain can also be treated with a combination of medications and minimally invasive interventions.[46] Tricyclic anti-depressants (TCA's) have proven useful in the management of chronic pain and specifically myofascial pain. NSAIDs (i.e. ibuprofen, naproxen) have had success in musculoskeletal pain, as long as comorbidities allow empiric use (e.g. renal disease, peptic ulcer disease). Opioid use is reserved for severe or refractory cases by consensus among providers as they are limited by efficacy, side effects, and potential for tolerance/dependence.[7,46]

Muscle relaxants can be used. However, a systematic review has shown that muscle relaxants increase adverse effects by 50% (relative risk of 1.50, 95% confidence interval, 1.14–1.98), including sedation, headaches, blurred vision, and dependence.[47,48]

Physical therapy is considered the cornerstone of treatment for musculoskeletal components of CPP because, as discussed above, muscle imbalances, bad posture, or alterations that affect load distribution in the pelvis are important sources of pain.[49] Close follow up should be scheduled with orthopedics in the case of pelvic fractures as it can take up to a year to completely heal, and the risk for sequelae is high.[5]

Therapeutic injections (e.g. 1%–2% lidocaine) directed at trigger points or with botulinum toxin can be attempted if the previous interventions fail in improving pain.[46,50] Targets include the obturator internus, piriformis, pubic symphysis, coccyx, the sacroiliac, or hip joint. In patients with concomitant neurogenic pain, lumbar or epidural injections can help in reducing the muscle spasm, in turn reducing the musculoskeletal source of pain. Therapeutic injections should be used along with other treatment modalities such as physical therapy.

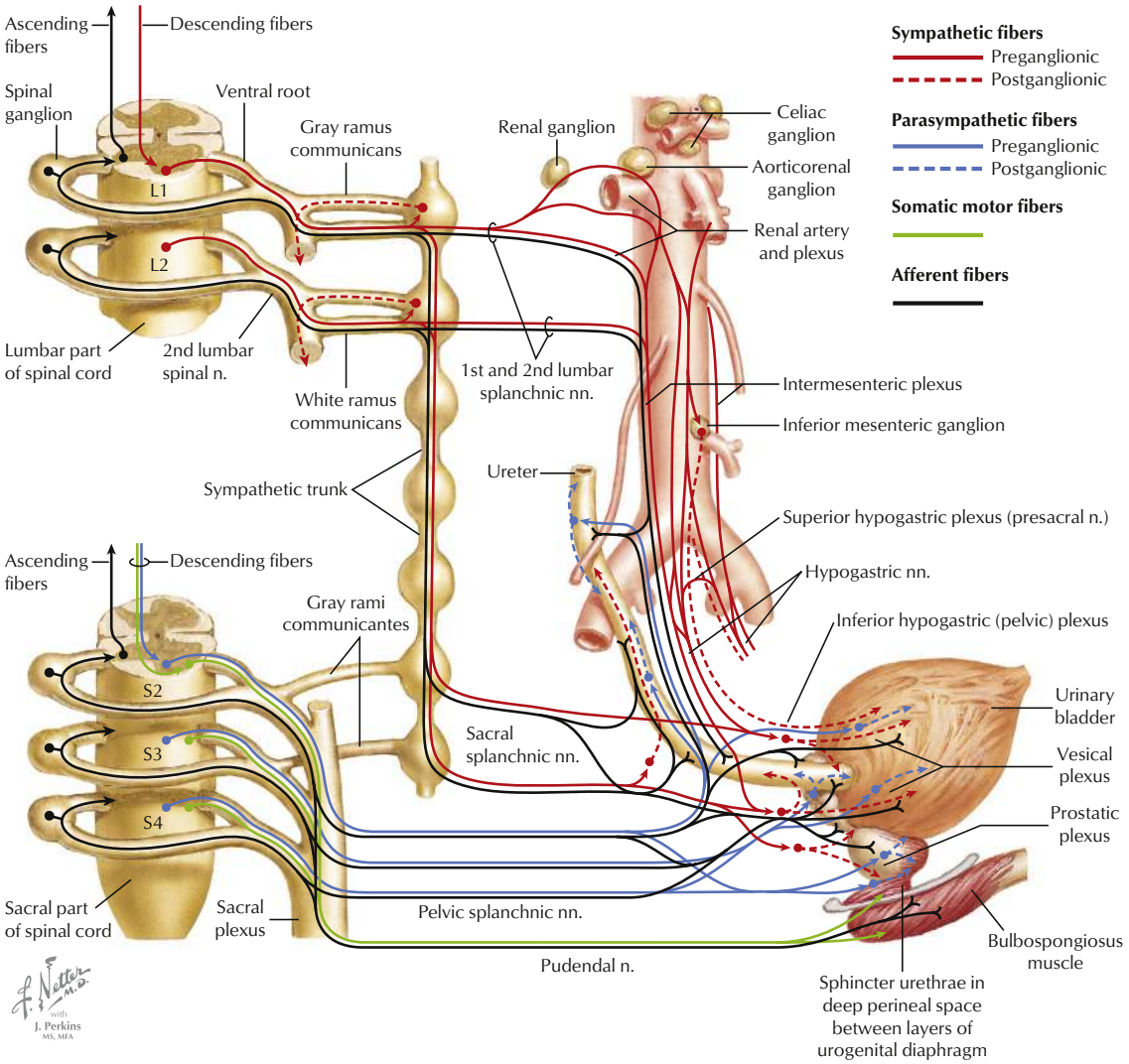
Focal Neurologic Conditions Causing Pelvic Pain

Neurologic causes of pelvic pain can arise anywhere in the nervous system. Conditions that affect the CNS or the peripheral nervous system, and systemic neuropathies, can manifest as CPP. This section will emphasize the focal neurologic etiologies of pelvic pain while exploring the more systemic causes of neurologic CPP later.

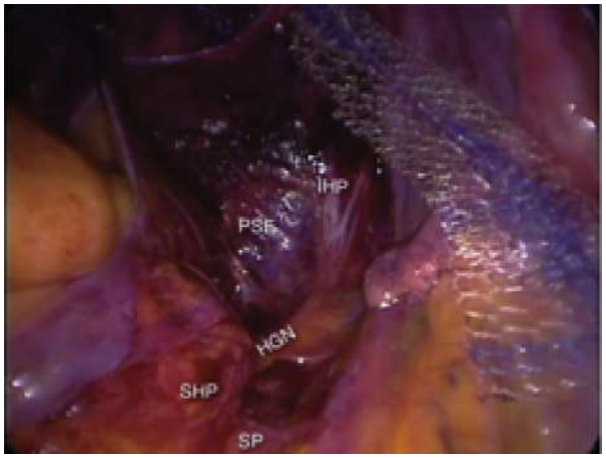
The pelvis is innervated by an array of nerve systems. The lumbar, hypogastric, and sacral plexuses are the main nerve groups innervating the pelvis.[51] They contain somatic and autonomic fibers (both parasympathetic and sympathetic). The somatic component is found within the lumbosacral, femoral, sciatic, obturator, and pudendal (arising from the nerve roots S2–S4), while the parasympathetic and sympathetic components arise from T12–L2 and S2–S4, respectively.[52] Fig. 42.7 illustrates the parasympathetic and sympathetic innervation of the abdomen, pelvis, and bladder.

The parasympathetic fibers (mostly the pelvic splanchnic nerves, aka the pelvic nerve or nervi erigentes) regulate the contraction of the bladder and rectum and relaxation of the sphincters. The preganglionic neurons are located in the sacral parasympathetic nucleus. Axon fibers from these neurons travel through the ventral nerve roots to the peripheral ganglia. Postganglionic neuron cell bodies are located in the detrusor wall and pelvic plexus (inferior hypogastric plexus). Therefore cauda equina or pelvic plexus injury is decentralized but not necessarily denervated. Sexual functions such as erection are also regulated by the parasympathetic splanchnic nerves. Sympathetic fibers (mainly from the superior hypogastric plexus) are involved in ejaculation, inhibition of the detrusor muscle, and the involuntary closure of the bladder neck.[53] Signaling is noradrenergic. The peripheral nerves involve the sympathetic chain ganglia, the inferior mesenteric ganglia, the hypogastric nerves, then the pelvic plexus (inferior hypogastric plexus) (Fig. 42.8). Voluntary sphincter control is somatic from the pudendal nerves, whose motor neurons are in Onuf's nucleus. Pelvic somatic fibers can be motor, sensory, or mixed; the main somatic nerves to consider are the obturator, pudendal, gluteal, genitofemoral, lateral femoral cutaneous, ilioinguinal, and femoral nerves. The interactions of these nerves are complex. For example, in urination, storage reflexes are maintained by parasympathetic low level firing and afferent firing from the pontine micturition center stimulating the spinal guarding reflex via sympathetic outflow, simultaneously inhibiting the detrusor and stimulating contraction of the bladder outlet, and pudendal outflow to the external urethral sphincter. Voiding reflexes are as follows: vesical afferent activity intensifies, activating the pontine micturition center. This inhibits the spinal guarding reflexes, stimulates high level parasympathetic outflow, and ascending afferents maintain the voiding reflex until the bladder is empty.

Lesions can result from direct damage (e.g. childbirth, surgery) or compression of the nerves from adjacent structures.[54]



• **Figure 42.7** Autonomic innervation of the pelvic floor. From: Netter Images. Available at: https://www.netterimages.com/innervation-of-the-urinary-bladder-and-lower-ureter-labeled-felten-2e-general-anatomy-frank-h-netter-29488.html.

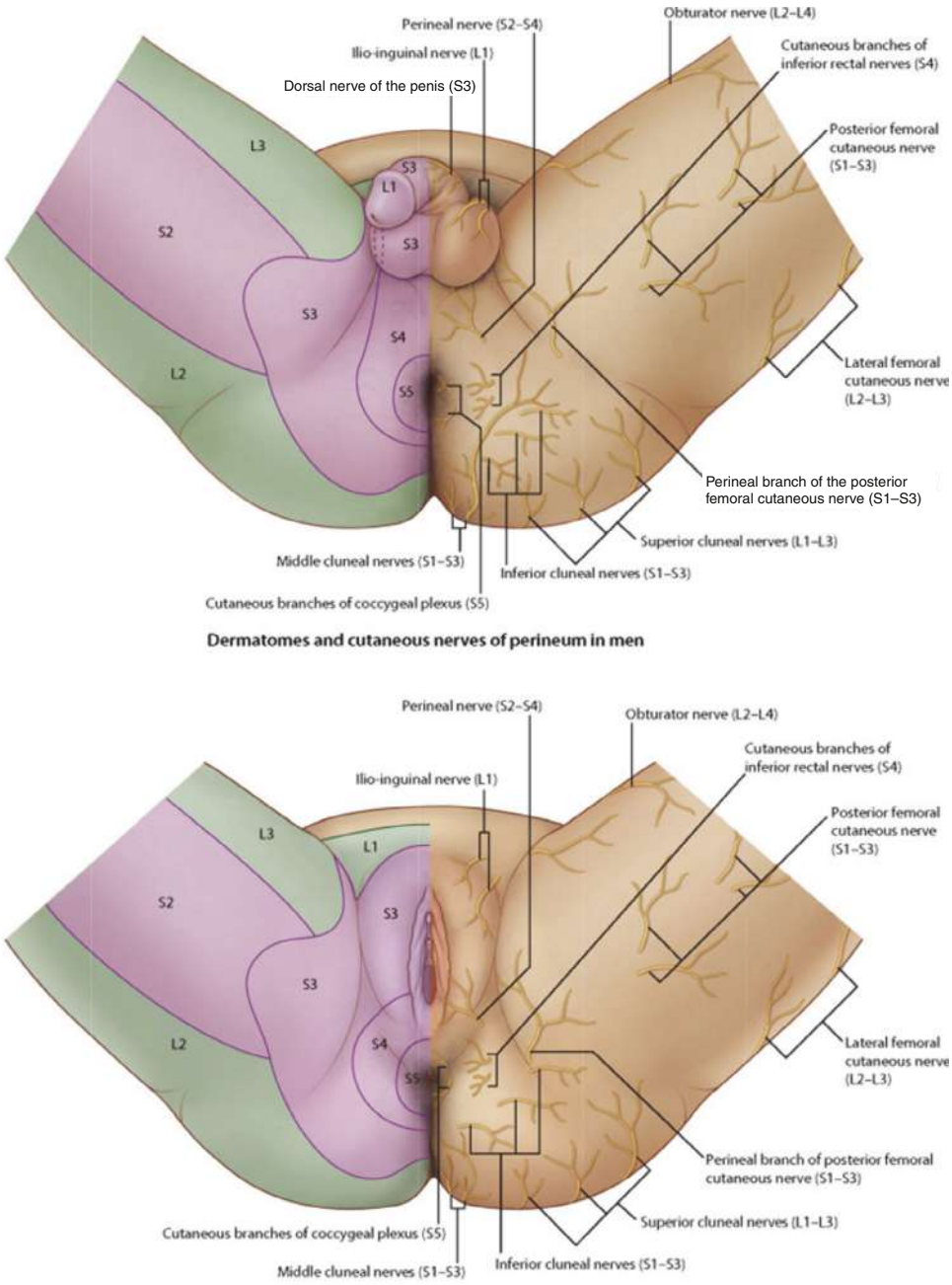


• **Figure 42.8** Photograph taken during laparoscopic abdominal sacrocolpopexy. Structures are labeled as follows: *IHP*, Inferior hypogastric plexus, *PSF*, pelvic splanchnic fibers; *HGN*, hypogastric nerve; *SHP*, superior hypogastric plexus; *SP*, sacral promontory.
Courtesy of Nucelio Lemos, MD PhD.

Neuropathies such as Small Fiber Neuropathies and infection (e.g. by herpes viruses) can also incur damage to the pelvic nerves.[5]

The sensory innervation of the pelvic structures is diffuse and demonstrates crosstalk, making it challenging to pinpoint a source of pain. Pain characteristics can help by suggesting whether it is visceral or somatic pain. Visceral pain arising from injury to visceral nerves is often described as dull, poorly localized, and is associated with autonomic symptoms (such as nausea).[51,55,56] Somatic pain results from nociceptive signals associated with tissue damage, while neuropathic pain is associated with neural damage at the level of the nerve, plexus, nerve root, or central nervous system. Neuropathic pain is associated with symptoms such as paresthesia, hyperalgesia, allodynia, or abnormal thermal sensations. Muscle weakness in the myotome of the affected nerve may also be seen. Fig. 42.9 illustrates the nerve distribution in the pelvis.

The most common causes of neuropathic pelvic pain because of peripheral nerve injury are discussed in Table 42.4. Pudendal neuralgia is the most commonly considered nerve entrapment in



• **Figure 42.9** Distribution of select nerves of the pelvis that may contribute to chronic pain. Perineal dermatomes showing the dermal distribution territories of the iliohypogastric, ilioinguinal, genitofemoral, femoral, pudendal, inferior cluneal, obturator, posterior femorocutaneous, lateral femorocutaneous, and the coccygeal plexus, which may present frequent anatomic variations and interconnections. Reproduced from Drake RL, Vogl A, Mitchell WA. *Gray's Atlas of Anatomy Elsevier*. Churchill Livingstone, London. 3rd ed. Philadelphia, PA: Elsevier; 2021:213–292.

the differential of pelvic pain. Direct compression of the pudendal nerve can occur at several levels, and non-mechanical causes of pudendal neuralgia such as viral infections or diabetes can also occur.[57] Location of a discrete lesion occurs at the sacrospinous/sacrotuberous ligaments in 42% of cases, Alcock's canal (medial to the obturator internus, within the fascia) in 26% of cases, and is at multiple levels in 17% of cases.[58,59] It can occur at the level of the piriformis, although the frequency is not reported. The more distal the lesion along the pudendal nerve, the less likely the anal region will be involved. Pudendal neuralgia presents with pain and dysfunction in the S2, S3, and S4 nerve distributions (including the rectum, genitalia, and urinary tract), sexual and sphincter dysfunction, and pain typically worse with sitting.[60] Nantes Criteria is used as a diagnostic tool for pudendal nerve pain.[61] Treatment is with neuromodulators, physical therapy, trigger point injection, botulinum toxin injection, neuromodulation, and in select cases, surgical release. Surgical release can be effective for decompression of discrete lesions. If pain has

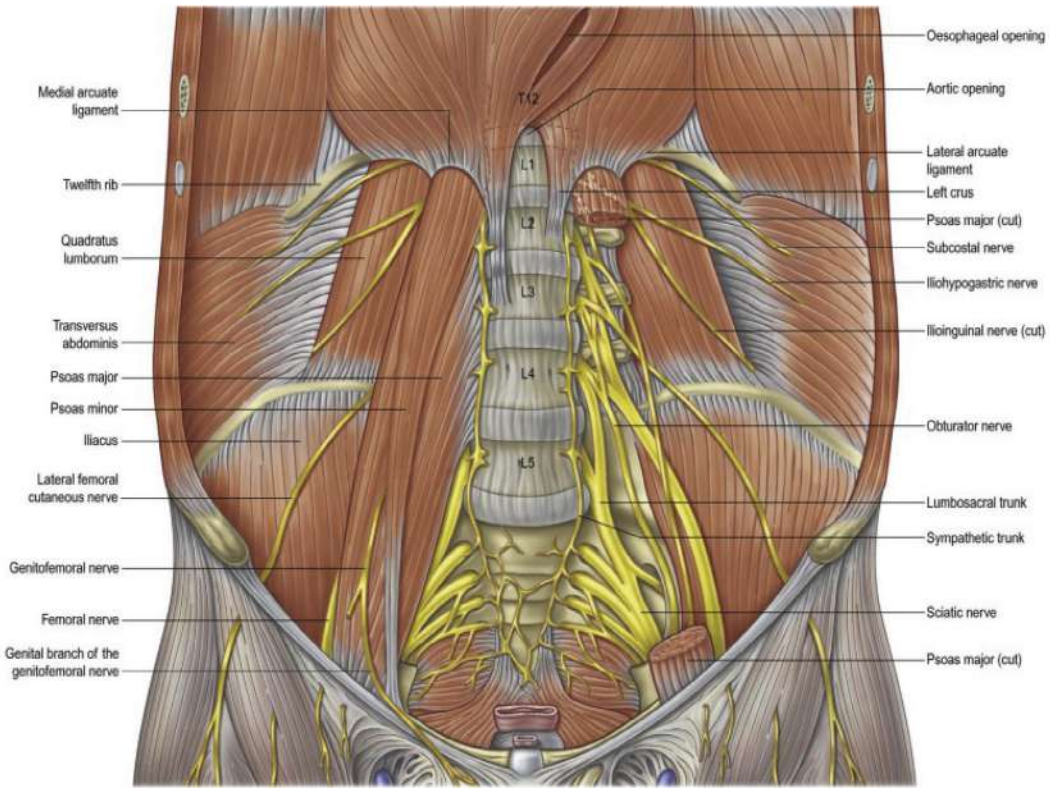
TABLE 42.4 Peripheral Nerve Injury Associated With Pelvic Pain and Dysfunction

Nerve Involved	Presentation
Ilioinguinal nerve (T12, L1)	Groin pain with radiation to the vagina, labia majora, root of the penis or upper scrotum, mons pubis, lateral waist.
Iliohypogastric nerve (T12, L1)	Lateral gluteal and suprapubic pain.
Obturator nerve (L2, 3, 4)	Pubic pain radiating to the inner thigh and knee. Weakness of adduction (adductors) and lateral rotation of the hip (gracilis muscle). Injury can occur during pelvic lymphadenectomy, deep endometriosis, dissection of the paravesical fossa, retzius space, or iliolumbar fossa.
Anterior abdominal cutaneous nerves	Abdominal pain usually lateral to the rectus sheath.
Lateral femoral cutaneous nerve (L2, L3)	Pain and numbness of the lateral thigh. Injury can occur secondary to obesity, tight pants or belts, or with impingement secondary to prolonged hip flexion.
S1 nerve root	Pain and numbness on the external aspect of the posterior thigh, calf, and leg and the exterior aspect of the foot. S1 nerve root entrapments can cause gait disturbances and loss of ankle stability.
S2 nerve root	Pain and numbness on the internal half of the posterior thigh, calf, and leg, internal surface of the foot, vulva, and clitoris (female), penis, and scrotum (male). Usually associated with urinary urgency and frequency. Genital arousal disorders, erectile dysfunction, and/or lack of vaginal lubrication may be present.
S3/4 nerve root *(usually entrapped together because of proximity)*	Pain and numbness on the buttock, anus, perineum, vulva, and clitoris (female), penis, and scrotum (male). Usually associated urinary and bowel urgency and frequency, pain on passing urine or stool. Often associated with vaginal and/or rectal foreign body sensation.
Sciatic nerve (L4, L5, S1, S2, S3)	Buttock, posterior thigh, calf, lateral leg, and foot pain. Impact on muscles of the posterior anterior and lateral compartments of the lower leg, foot drop. Lies 2 cm from the sacrospinous ligament and can be injured during sacrospinous ligament vault fixation. Hip replacement, and even improperly performed buttock injections.
Genitofemoral nerve (L1, L2)	Genital branch: Pain in the inguinal fold, mons pubis, base of the penis, labia majora, anterior vulva, clitoris, and urethra femoral branch: superomedial thigh. Injury can occur during, e.g. pelvic lymphadenectomy or psoas hitch.
Pudendal nerve (S2, 3, 4)	Pain and dysfunction in the S2, S3, and S4 nerve distributions (which includes the rectum, genitalia, and urinary tract, urethra), Urgency or pain associated with urination or bowel movement, sexual and sphincter dysfunction (erectile dysfunction, lack of lubrication), and pain that is typically worse with sitting. It can be an injured surgical leg. During sacrospinous ligament vault fixation, because of infection (e.g. herpes) or entrapped by a hypertonic muscle.
Posterior femoral cutaneous nerve and inferior cluneal nerves	Inferior gluteal (buttocks) pain.
Autonomic nerves Sympathetic: superior hypogastric plexus, hypogastric nerves, inferior hypogastric plexus Parasympathetic: pelvic splanchnic nerves, inferior hypogastric plexus, visceral nerve branches	Injury to the sympathetic nerves can lead to urinary incontinence and urgency. The hypogastric nerves can be encountered during sacral dissection. Injury to the parasympathetics can lead to atonic bladder, reduced bladder and rectal sensation, decreased vaginal blood flow, and lubrication. Abdominoperineal resection or application of mesh for prolapse can injure the inferior hypogastric plexus and rectal plexus visceral nerve branches, respectively.

Adapted from *Facing Pelvic Pain.*[5]

been present for fewer than six years, 66% of patients improve. If >6 years, 40% improve.[59] Another pathologic condition, sacral radiculopathy, can present with similar symptoms and is often confused with pudendal neuralgia.[62] Symptoms exclusive to sacral radiculopathy include the addition of back pain, gluteal pain, and sciatica. The most common causes include surgical damage, compression by varicose veins, endometriosis, sacral tumors, tethered cord, and Tarlov cysts.[63] Pudendal neuralgia is but one of many peripheral nerve lesions that cause pelvic pain. Please refer to Table 42.4 for diagnostic guidance. Figs. 42.10–42.12 illustrate the pelvic nerve, cutaneous nerves, and dermatomes.

Lesions within the spinal cord can result in injury to the nerve fibers, which can present as pelvic pain (Table 42.5). CPP in patients with spinal cord pathologies can be especially prevalent. One study in the United States reviewed 1,295 patients with spinal cord injury and approximately 25% of the cohort presented with chronic pain throughout the pelvic girdle.[62] Tumors, Tarlov cysts, disk herniations, and tethered spinal cord are causes of neurologic pelvic pain originating in the spinal cord (Fig. 42.13). Symptoms such as cauda



• **Figure 42.10** The lumbosacral plexus. These peripheral nerves (nerves that connect the spinal cord and brain to the limbs and organs) innervate many structures in the pelvis, although some of them originate outside of the pelvis. Reproduced from Standring S. *Gray's Atlas of Anatomy. The Anatomical Basis of Clinical Practice*. 41st ed. Elsevier; USA, 2016:1083–1097.e2. Figure 62.14.

equina syndrome can present acutely, including bowel or bladder dysfunction, saddle anesthesia, bilateral sciatica, and leg weakness. This is most commonly caused by a tumor or midline disc and is considered a medical emergency. Other causes of cauda equina syndrome include abscess, arachnoiditis, tethered cord, chronic inflammatory demyelinating polyneuropathy, herpes simplex and zoster, Lyme disease, and tuberculosis.[5] Pathology within the brain itself can also lead to pelvic pain, especially through central sensitization of pain. This concept is discussed further in the chapter.

The diagnostic approach to the neurogenic cause of pelvic pain is via full genital and neurologic exam. History should focus on risk factors such as pelvic or abdominal surgeries, thrombosis, obstetric history, and pathologies of the CNS. It is important to note the characteristics of pain, timing, quality, intensity, and the presence of radiated or referred pain. The physical exam should assess for muscle strength, muscle tone, and range of motion. Sensation is assessed in all the dermatomes of the lumbosacral region. Proprioception, vibration, and reflex testing should also be performed. Focality or multifocality, upper versus lower motor neuron findings should be recorded.

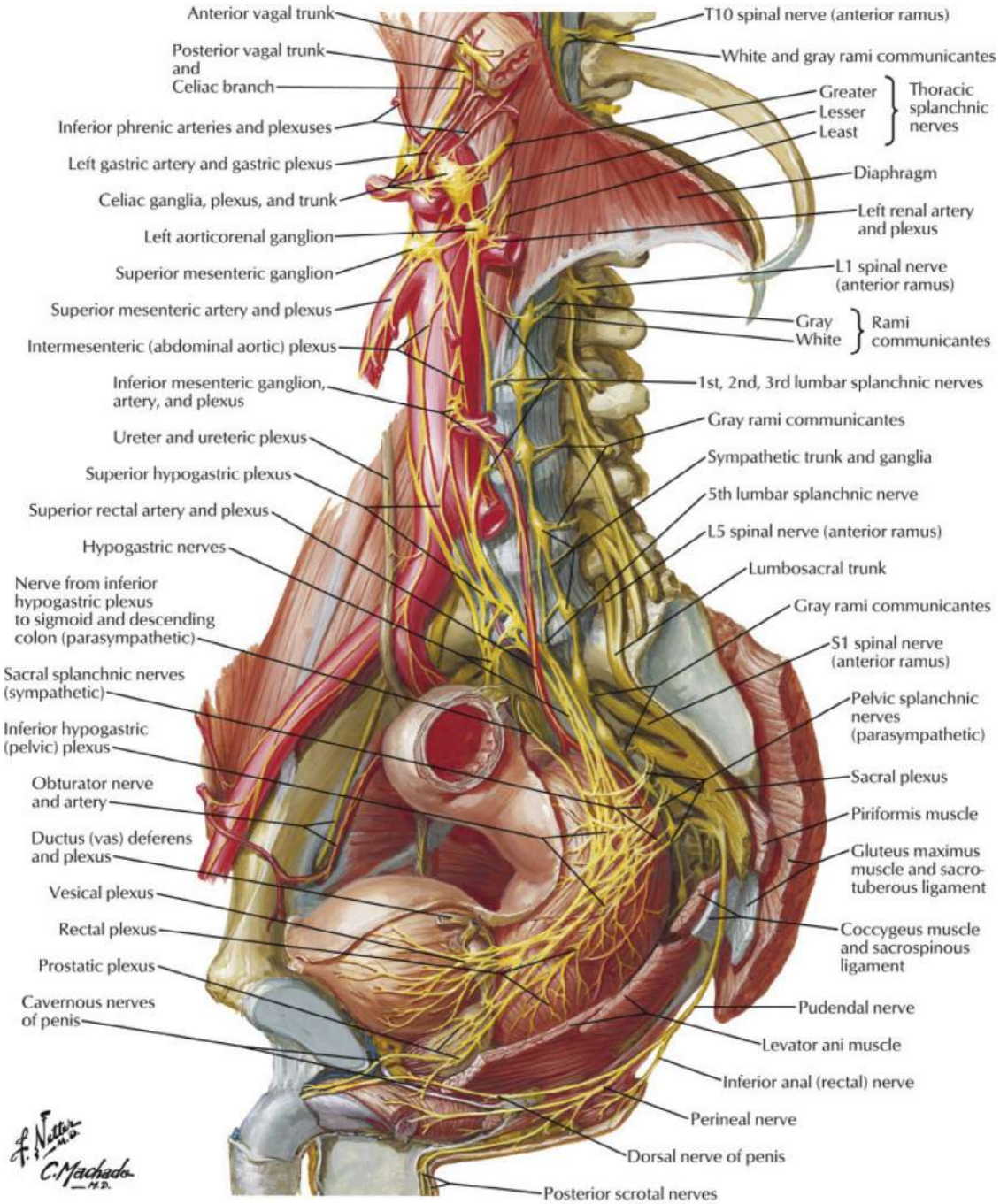
Some pathologies, e.g. pudendal, abdominal wall, or sacral neuropathies, can be diagnosed effectively with a selective nerve block.[51] Additional tests such as ultrasound or urodynamic testing (bladder function), defecography (bowel function), and electromyography (EMG) can help in determining the cause. It is important to note that standard physical exams and EMG assess only the large nerve fibers. Small fiber neuropathy, discussed further below, requires quantitative sensory (mechanical and thermal) testing for diagnosis.

There are several treatment options in the management of neurogenic pelvic pain, ranging from conservative physical therapy to invasive procedures. Physical therapy alone remains controversial in the management of radicular pain, particularly in the acute setting, as some studies have noted no difference in outcome between physical therapy and rest.[64,65]

Medical treatment includes NSAIDs, acetaminophen, or serotonergic compounds. It is of note that their lack of selectivity for neurologic processes might limit their efficacy in the most severe cases. Opioids can be effective in the management of these patients; however, special attention should be made to avoid the development of tolerance and opioid-induced hyperalgesia, and most recommend their use primarily in the acute setting.[66,67] The development of side effects and dependence also limit opioid use. Pregabalin has been proven effective in the management of pelvic pain of neurologic cause as it reduces neuronal hyperexcitability in the spinal cord and suppresses hypersensitivity in visceral pathways.[68]

It has been argued that if etiologic treatment is possible, it should take priority over solely medical symptomatic treatment.[51] Targeted therapies such as therapeutic injections, either directed at a single nerve (e.g. local anesthetics, glucocorticoids, botulinum toxin) or as epidural injections (e.g. steroid injections), have proven very effective.[66,69] Other therapies such as neurolysis, nerve decompression surgery, or neurosurgical or spinal procedures are also effective in management for specific indications.

Neuromodulation has had considerable success in the treatment of refractory pelvic pain, with improvement seen in 50% up to around 90% of patients presenting with CPP, depending on



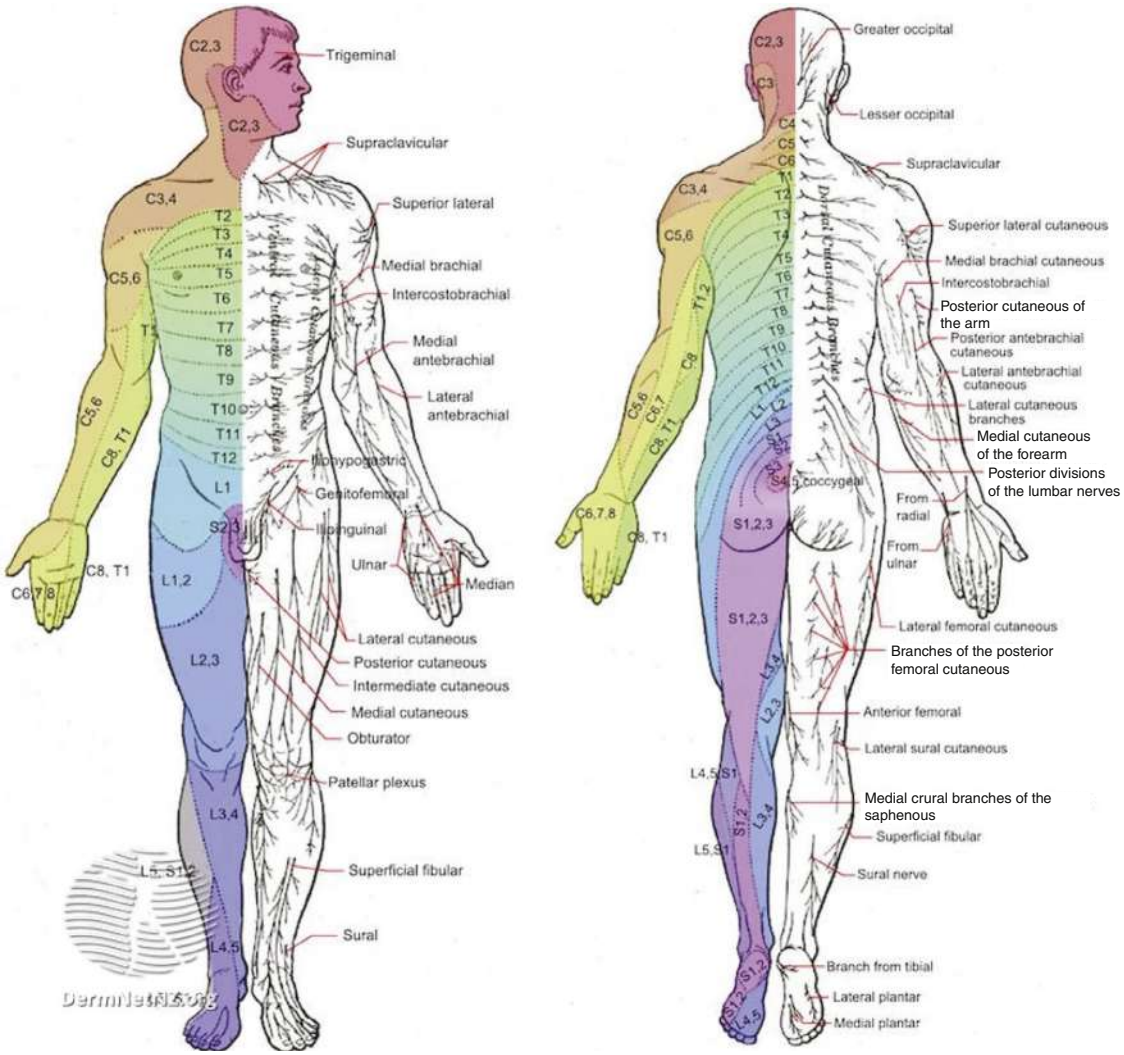
• **Figure 42.11** Nerves of the pelvic viscera (male). Reproduced from Netter FH. Plate 392. *Atlas of Human Anatomy*. 2018: pp. 36.

the modality of neurostimulation performed.[70] Examples include spinal cord stimulation, nerve root stimulation, and pudendal nerve stimulation. Motor cortex stimulation is also an approach that can be attempted in cases refractory to other neurostimulation modalities.[71]

Vascular Causes of Pelvic Pain

Vascular causes of pelvic pain can stem from either venous or arterial disorders. Most of the arterial supply of the pelvis arises from the internal iliac artery and its numerous branches. The pudendal artery supplies the perineum, the buttock region is supplied by the gluteal arteries, and the pelvic organs are supplied by the vesical, rectal, and uterine arteries (in the case of females).[72] The veins that arise from the pelvis mostly drain into the internal iliac vein. The major exceptions are the gonadal arteries and veins, which arise from the abdominal aorta and drain into the inferior vena cava (IVC).[73] It should be noted that the left gonadal vein drains into the left renal vein prior to the IVC. Figures 42.14 and 42.15 illustrate the vascular structures present in the pelvis.

Although arterial etiologies are a rare cause of pelvic pain, these disorders should be ruled out if the context suggests their presence,



• **Figure 42.12** Cutaneous nerves and dermatomes. Submitted request for permission 8/1/20. Available at: https://www.dermnetnz.org/permission/image/42666, https://www.dermnetnz.org/topics/dermatomes/Credit: https://www.grepmed.com/images/2963/dermatomal-dermatomes-diagnosis-cutaneous-anatomy-nerves-roots.

TABLE 42.5 Central Nervous System Causes of Pelvic Pain

Spine Diagnosis	Symptoms	Physical Exam Finding
Herniated disc: disc protrusion causes spinal cord or nerve root compression.	Back pain, shooting pain or numbness that follows a specific dermatomal pattern (e.g. a T10 through L1 disc herniation may radiate into the skin of the groin or abdomen), or sciatic symptoms in the leg; persistent genital arousal disorder has also been attributed to the spine.	Abnormal gait, pain with provocative maneuvers (e.g. pain with low back flexion, positive straight leg test that radiates pain with spine range of motion), possible increased or decreased reflexes.
Tarlov cysts: fluid-filled nerve root cysts found most often at the sacral level of the spine; small cysts may be a normal variant and are present in 5%–10% of people.	Symptoms vary but may present with pain over the buttocks and sacrum or with bowel, bladder, or sexual dysfunction.	Pain with sitting, standing, or walking; may have increased sensitivity or loss of sensitivity to touch over the sacrum and buttock; may present with lower extremity weakness.
Spina bifida occulta.	Typically *asymptomatic* but may cause lower extremity symptoms, including weakness, and urinary, sexual, or bowel symptoms, pelvic pain, and impaired sensation of the genitals, bladder, or bowels. Sometimes symptoms begin during growth spurts because of an associated *tethered spinal cord.*	May present with lower extremity weakness; the skin over the spine may present with an abnormal tuft of hair, dimple, or birthmark.

Continued

TABLE 42.5 Central Nervous System Causes of Pelvic Pain—cont'd

Spine Diagnosis	Symptoms	Physical Exam Finding
Tethered spinal cord: caused by tissue attachments that limit the movement of the spinal cord within the spinal column; these attachments cause an abnormal stretching of the spinal cord, and therefore upper and lower motor neuron findings can be present; associated with spina bifida.	Back pain or shooting pain in the legs, weakness or numbness in the legs, lower extremity spasms, bowel or bladder dysfunction (over or underactive).	Lower extremity weakness, abnormally low or high reflexes, diminished lower extremity sensation. Gluteus or calf atrophy.
Cauda equina syndrome: caused by central spine nerve compression, such as stenosis in the lumbar region from a large herniated disc or tumor.	Symptoms may include severe lower extremity weakness and/or pain, decreased sensation in the legs and/or the lower pelvic region *("saddle anesthesia"),* new-onset difficulty urinating or sudden urinary incontinence, and stool incontinence. If the above symptoms are acute, they require emergency evaluation.	Lower extremity weakness, reduced or absent reflexes in the legs, gluteus, or atrophy if chronic.
Sacral tumor: benign or malignant growths around the sacral nerve roots.	May present with symptoms similar to Tarlov cysts and herniated discs, such as back pain, lower extremity pain, lower extremity weakness, numbness or tingling, rectal dysfunction, urinary retention or incontinence, erectile dysfunction.	May present with tenderness over the sacrum or lower extremity weakness. A mass may be felt in the sacral area. Gluteal and calf atrophy may be present.

Adapted from *Facing Pelvic Pain.*[5]

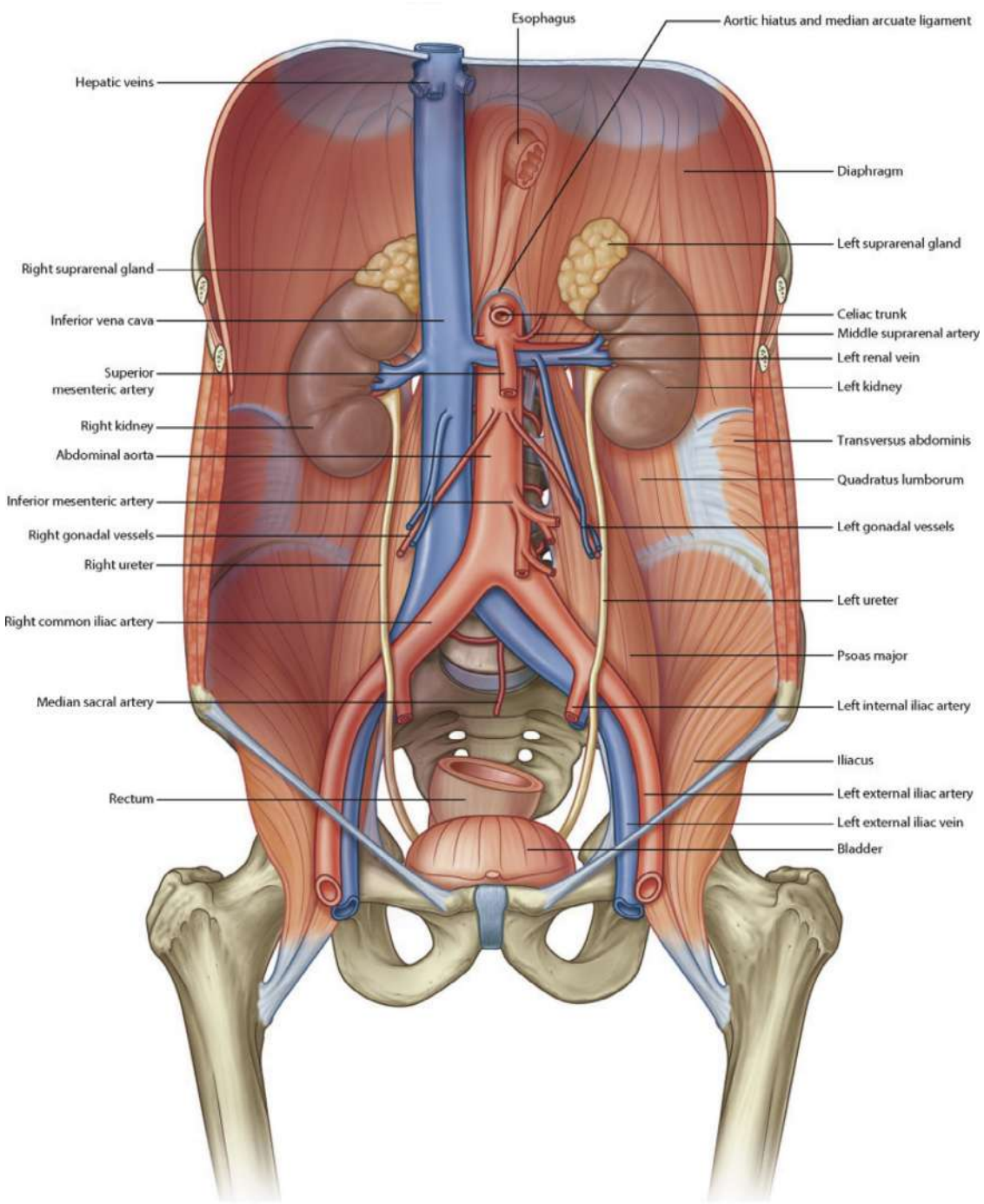
• **Figure 42.13** Sacral tumor affecting bladder function, gait, and muscle tone visually. Patient also reported radicular pain, fecal incontinence, and erectile dysfunction. Courtesy Elise De, MD.

namely because vasculitis and ischemic disease can have serious implications.

Vasculitis is a rarely identified cause of pelvic pain and can be difficult to diagnose because of the non-specific signs and symptoms it presents, as it can affect any blood vessel in the body. In these disorders, the vessel wall is infiltrated by white blood cells with resultant inflammatory reaction. Vasculitis can arise either as a primary disorder or secondary to another process and can occur because of a systemic disease or as single organ vasculitis. Both can cause CPP.[74] Single organ vasculitis (SOV) can be either the first presentation of systemic vasculitis or a local inflammatory reaction to injury (e.g. tumors or pelvic surgery), with the latter being most common.[75,76] The progression of true SOV to systemic vasculitis is uncommon (less than 1%) and often requires just symptomatic management beyond the treatment of the underlying diagnosis.[77] Often, the precise cause of vasculitis remains unknown, but etiologies include autoimmune or rheumatic disorders, reaction to a medication, or infection. There is still an ongoing effort to develop a universal classification for vasculitis, but it is usually classified according to the size of the vessels involved (i.e. small, medium, and large sized vessels). Among the systemic vasculitides, giant cell arteritis (GCA; previously, temporal arteritis) is most prevalent in patients with pelvic pain. The classic symptoms of GCA include headaches, vision loss, jaw claudication, scalp tenderness, muscle stiffness, and pain.[78] The high level of association between GCA and polymyalgia rheumatica (PMR) plays a role in the presentation of pelvic pain. Around 50% of patients with PMR have been documented to have concomitant GCA by biopsy. Pelvic girdle pain occurs bilaterally in these circumstances and is present in about 50%–70% of patients afflicted by PMR.[79,80] It is important to have a high level of suspicion when diagnosing pelvic pain because of GCA, secondary to its potential to cause blindness. Other examples of systemic vasculitides which can cause pelvic pain include the following:

Large Sized Vessels

- Takayasu's arteritis, a large-vessel vasculitis that affects the aorta, with major branches to the extremities, and sometimes internal organs, usually occurring in females under 50 years
- Giant/temporal cell arteritis, already discussed above

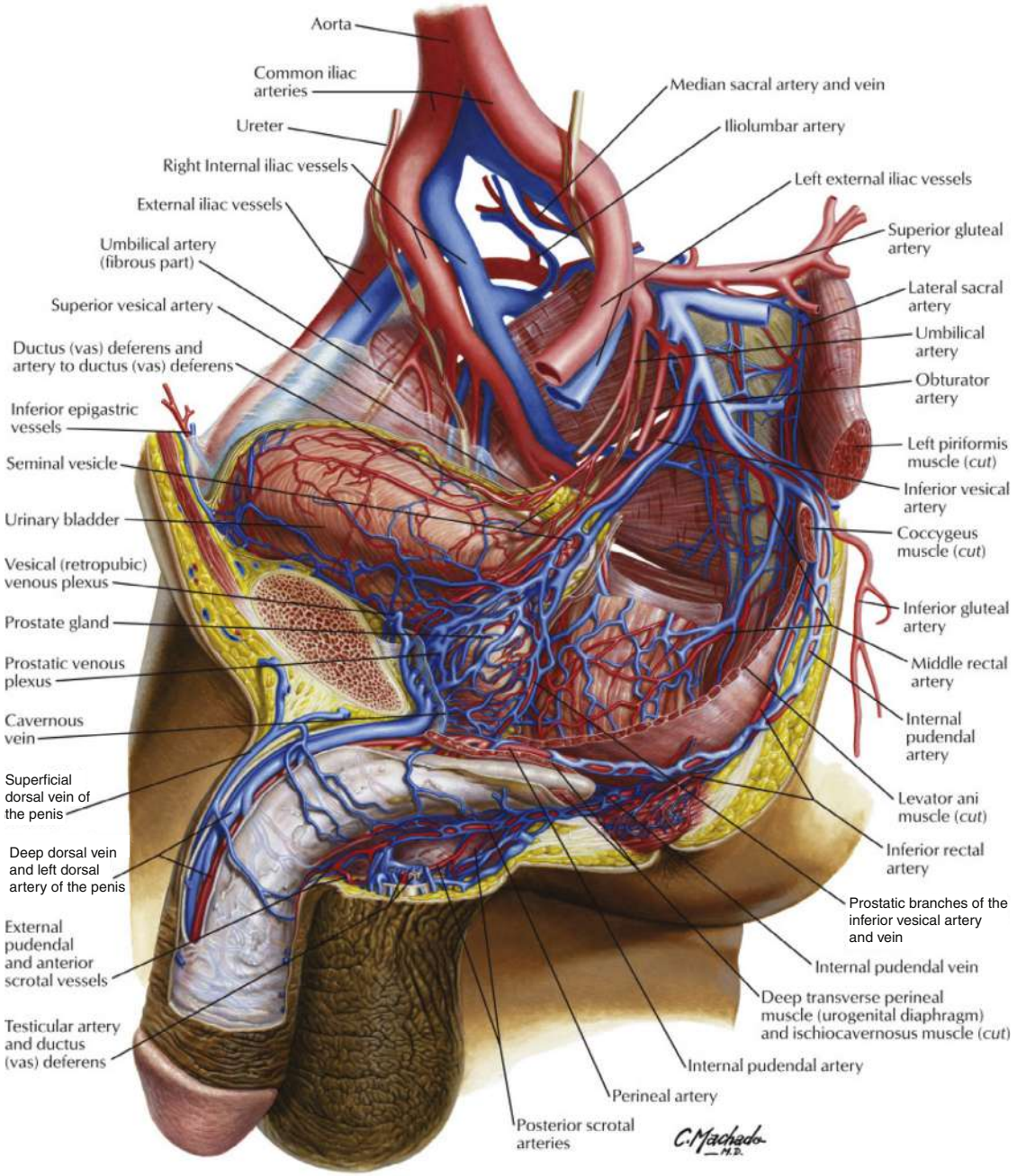


• **Figure 42.14** Vessels of the posterior wall. From: Drake RL, Vogl A, Mitchell WA. Gray's Atlas of Anatomy, 2021, pp. 133–212.

Small- and Medium-sized Vessels

- Granulomatosis with polyangiitis (GPA), formerly known as Wegener's, which is a systemic disease that involves the lungs, kidneys, upper respiratory tract, and other organs associated with the autoantibody ANCA.
- Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg Strauss, which is associated with asthma, nasal polyps, sinusitis, elevated eosinophil counts, and vasculitis and tends to involve the lungs, peripheral nerves, skin, kidneys, and heart.
- Microscopic polyangiitis: A systemic vasculitis affecting small and medium-sized blood vessels also associated with ANCA.
- Polyarteritis nodosa: The prototype of systemic vasculitis involving many different organ systems such as the intestines and kidneys.

The less common causes of vascular CPP, such as vasculitis, should be suspected in patients with systemic symptoms and evidence of organ dysfunction, while ischemic disease should be ruled out in patients with risk factors for peripheral artery disease.[81]



• **Figure 42.15** Plate 385 arteries and veins of the pelvis: male. From: Netter FH. Plate 385. *Atlas of Human Anatomy*. 2018: 367–44D1.e11.

Laboratory studies such as C-reactive protein or erythrocyte sedimentation rate are of particular aid in diagnosing vasculitis. Doppler ultrasound has been found to have a sensitivity ranging from 70%–92% and a specificity of around 96% for the diagnosis of GCA.[82,83] For the diagnosis of congestive pelvic venous disorders, venography (either by CT or MRI) is considered the gold standard, often demonstrating pelvic varicosities. Venous duplex/Doppler ultrasound is also used.

Treatment of vasculitides usually includes the administration of corticosteroids (dosing of 40–60 mg per day) with a more aggressive approach in the setting of visual symptoms such as in GCA (intravenous [IV] methylprednisolone, 1 g daily for the first three to five days).[84] However, because of adverse effects of long-term corticosteroid dosing (up to 85%), steroid-sparing agents such as tocilizumab or abatacept are under research and have shown promise in early trials.[83]

While rare in the context of CPP, ischemic disease can present as pain within the pelvic girdle. The abdominal aorta and the bifurcation of the common iliac arteries is a common place for atherosclerotic plaques to form, affecting pelvic blood flow.[85] Chronic pelvic ischemia affects mainly the perfusion of the lower urinary tract. Ischemia in this region can precipitate the development of an overactive bladder, bladder pain syndrome, and associated sexual dysfunction can be present.[86,87] Little has been written about the treatment of ischemic disease as a source of CPP, possibly because other manifestations of the disease are

taking clinical precedence. Treatment should revolve around lifestyle changes such as smoking cessation. The addition of cardiovascular mortality-lowering medication, such as clopidogrel and aspirin, could be considered. Cilostazol is an effective medication for symptom control in intermittent claudication as it helps with vasodilation, but little information is available concerning chronic pelvic ischemia. Medications such as silodosin, tadalafil, mirabegron, and melatonin have been found to produce protective urodynamic parameters for bladder function in these patients, but further studies are needed.

Pelvic venous disorders: Pelvic venous disorders have been cited as one of the most common causes of CPP, with figures as high as 31% of all CPP cases in females.[7,88] They are more common in multiparous, premenopausal females. The complicated interplay of the pelvic venous vasculature and vague symptomatology has made it difficult to approach these disorders; it has been proposed to look at them as three interconnected systems: the renal and gonadal veins, the iliac veins, and lower extremity veins. Pain originating from venous disorders is most likely because of venous hypertension arising within these systems. The constellation of different signs and symptoms depend on what venous reservoir the venous pressure is being transmitted to (renal hilar, pelvic, or leg). The clinical manifestations include pelvic pain, pelvic varicosities, leg varices, and symptoms related to renal venous hypertension (e.g. hematuria, left flank pain).

This increase in pressure usually is from primary or secondary insufficiency of the left gonadal vein, left renal vein (LRV), or the common iliac veins (CIV). Primary insufficiency of the pelvic veins can be congenital or acquired. In contrast, secondary insufficiency arises from pathologies such as nutcracker syndrome (compression of the LRV by the superior mesenteric artery) or May-Turner syndrome (usually compression of the left CIV by the left internal iliac artery).[88]

The diagnosis of a vascular cause of pelvic pain relies on a combination of the patient's history, physical examination, and ultimately imaging studies. Questions should be directed at identifying the timing of pain onset and its characteristics. Pain arising from pelvic venous disorders is typically described as dull, throbbing, and achy. It arises or becomes worse when standing for long periods and is usually relieved when in a supine position. There can be a cyclic component. Low back pain, dyspareunia, and bladder and bowel symptoms may be present. The pain is often worse during menstruation, prolonged standing, or intercourse and is described as aching, throbbing pressure, or cramping. This condition is more common in females who have given birth, and the left side is more often affected because the left gonadal vein inserts into the LRV (or in the case of May-Turner, the configuration of the left common iliac vein with respect to the artery). The physical exam in females should assess for ovarian point tenderness or cervical motion tenderness: ovarian point tenderness on examination with a history of postcoital ache has been reported as 94% sensitive and 77% specific for pelvic congestion syndrome (PCS).[89] The presence of varicosities in the lower extremities, the vulvoperineal region in the case of females, or varicoceles in the case of males should be documented. Moreover, 33% of those with PCS have vulvar varicosities (hemorrhoids or varicosities of perineum, vulva, buttocks), and 90% have lower extremity (LE) varicosities. However, of note, only 5% of those with LE varicosities have PCS. Imaging may show pelvic varicosities on ultrasound. MR Venography is considered diagnostic and will show dilation, most commonly of the left gonadal vein.[90,91]

Endovascular or surgical approaches are the best options for the management of pain stemming from pelvic venous congestion. Medication treatment with medroxyprogesterone or goserelin has been tried in females on the basis that pelvic venous vasculature is highly respondent to estrogens, but no sustained relief has been achieved, and the adverse effects are significant.[92] Surgical management, including ovarian vein resection or hysterectomy, is practiced, but is invasive, carries a risk of hemorrhage given the dilated vasculature, and is associated with high relapse rates (up to 33% in hysterectomy). For venous valvular incompetence/reflux, endovascular procedures include simple coil embolization, glue embolization, or sclerotherapy to manage reflux in the primary ovarian and internal iliac veins. Endovascular stenting has also been found to be beneficial in compressive syndromes such as May-Turner and Nutcracker Syndromes.[7] In May-Turner Syndrome, angioplasty followed by stenting may be considered as the first treatment option before embolization of dilated pelvic veins or formal surgical approaches. Following iliac venous stenting, pain relief and resolution of dyspareunia resolved in 80% one year after the procedure.[93] In nutcracker syndrome, there is more robust data regarding formal surgical repair (LRV transposition) with the resolution of symptoms in 87% of patients at a mean follow up of 37 months.[94,95] Endovascular stenting shows promise. However, data is lacking thus far, and stent migration, embolization to the right heart, and thrombosis have been described.

Systemic Causes of Pelvic Pain

It can prove useful to evaluate systemic diseases, as sometimes CPP can manifest a larger process occurring within the body. A fundamental concept guiding evaluation is to determine whether pain is localized to the pelvic or whether the patient presents with multiple coexisting pain syndromes. Some of the established systemic causes of CPP are briefly discussed.

Neurologic

As discussed, CPP can have a neurologic component involving direct or indirect injury to the central and peripheral nervous systems. However, some systemic neurologic diseases can present with widespread pain; the numbers range between 20% and 40% in patients afflicted by a primary neuronal disorder.[96]

Alterations within the structure and chemistry of the brain result in an aberrant communication among sensory, modulatory, cognitive, and emotional systems. These changes can precipitate pain in patients even when peripheral stimuli are no longer present. Complex regional pain syndrome is an example, as a small injury in a peripheral nerve induces changes at the thalamic and subthalamic level and can even include changes in the parietal lobe and basal ganglia.

Other CNS disorders such as Parkinson's disease, Alzheimer's disease, stroke, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) can present with widespread pain, in some cases with high rates of prevalence. In MS, for example, widespread pain is reported in as many as 86% of patients.[97] In Parkinson's disease, pain is present in approximately 40% of patients, in some noted as the major complaint, even ranking above motor symptoms.[98] Prevalence is also considerably high in Alzheimer's disease (57%), stroke (particularly if the thalamus is affected) (8%–14%), and ALS (15%).[99–101] Management can be attempted with pharmacologic treatment (e.g. anti-epilepsy drugs, anti-depressants, and membrane stabilizers), brain stimulation techniques, or even targeted delivery of medication to the CNS using CT or MR imaging.

Peripheral neuropathy is essential to consider when evaluating patients with pelvic pain, particularly when CPP is refractory to intervention or occurring in concert with other pain syndromes. Peripheral neuropathy is experienced by approximately 40 million people in the United States. Many peripheral neuropathies are mixed neuropathies with both large fiber and small fiber involvement (Table 42.6). Increasingly recognized is the demonstration of specific involvement of small myelinated or unmyelinated fibers, e.g. small fiber neuropathies.[102]

In our population of complex pelvic pain patients (refractory or multisystem pain), 64% (25 of 39) had a skin biopsy positive for small fiber polyneuropathy. Comorbid conditions included gastroesophageal reflux disease in 46%, migraine in 38%, IBS in 33%, lower back pain in 33%, fibromyalgia in 38%, endometriosis in 15%, interstitial cystitis in 18%, vulvodynia in 5%, and other chronic pain syndromes in 36%.[103] Of note, in separately published studies, approximately 50% of patients who have been diagnosed with fibromyalgia in several published studies have demonstrated findings consistent with small fiber polyneuropathy (SFPN) on diagnostic biopsies.[104,105] Muscle cramps can be a symptom of SFPN. Small fiber neuropathies (SFN) occur when injury to the peripheral nerves predominantly or entirely affects the small myelinated (Aδ) or unmyelinated C fibers. The fibers affected include both small somatic pain fibers and autonomic fibers. Thermal perception and nociception, enteric function, cardiovascular, genitourinary, perspiratory, lacrimal, and salivary gland function are subserved by small fibers.[106]

Most SFNs occur in a length dependent fashion, first stocking distribution changes and later glove distribution. Less common but no longer rare, non-length dependent SFN can result in symptoms involving the face, trunk, proximal limbs, or other more localized areas such as the pelvis. The pathogenesis of injury to small fibers is not well understood and can progress to involve the myelinated and therefore better protected large fibers. Epidemiologic data from the Netherlands suggest a minimum incidence of SFPN of 12/100,000 people.[107] Children can also experience SFN. Disorders associated with SFPN include diabetes, sarcoidosis, thyroid dysfunction, vitamin B12 deficiency, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, systemic lupus erythematosus, amyloidosis, Ehlers Danlos Syndrome, hereditary sensory and autonomic neuropathies, alcohol use, Lyme disease, metronidazole, statins, and celiac disease/gluten intolerance.

TABLE 42.6 Large and Small Fiber Polyneuropathies

	Large Fiber Neuropathy	Small Fiber Neuropathy
Symptoms	Numbness, pins and needles, tingling, poor balance	Pain: burning, electric shocks, stabbing pain, numbness
Exam findings	Reflexes, proprioception Vibration, +/– motor	Thermal, pinprick sensation, allodynia
Functional changes	Pressure, balance, fall risk	Nociception; protective sensation
Diagnostic test	EMG/NCV, sural nerve biopsy	QST, nerve biopsy, Intraepidermal nerve fiber density (skin biopsy)

Symptoms vary widely in severity. Often affected individuals describe a gradual onset of vague distal sensory disturbances, for example, feeling like there is sand in the person's shoe, a sock feeling as if it has pebbles in it, pins and needle sensations, cold painful sensations or tingling, burning pain in the extremities, allodynia, and hyperesthesia. Socks or bedsheets on the feet may be painful. Symptoms are often worse at night. Autonomic and enteric dysfunction may be present, including dry eyes, dry mouth, lightheadedness with changes in posture, syncope, abnormalities of sweating, erectile dysfunction, gastrointestinal symptoms such as nausea and emesis, constipation, diarrhea, and changes in urinary frequency, including nocturia. Diagnosis is by history, quantitative sensory testing (QST), skin biopsy, and autonomic testing. The neurologic examination (which assesses large fibers) may be normal. However, possible findings include decreased pinprick, diminished thermal sensation, hyperalgesia, or dry skin. Autonomic (tilt-table) testing may show abnormal heart rate responses to deep breathing, heart rate and blood pressure responses during Valsalva maneuvers, heart rate and blood pressure response to a 70-degree tilt, and sudomotor responses (sweat production). The standard biopsy is a 3 mm skin punch biopsy that can be taken from anywhere over the body. Because of the need to compare to normal values, the LE 10 cm proximal to the lateral malleolus is most commonly assessed (of relevance, length dependent SFN is more common than non-length dependent). The results are expressed as the number of intraepidermal fibers per mm. The sensitivity (78%–92%) and specificity (65%–90%) are fairly high for this technique.[106] Once diagnosed, workup depends on the suspected cause: metabolic, nutritional, infectious, autoimmune, allergic, paraneoplastic, neurotoxins, or hereditary. Lumbar puncture may be indicated if inflammatory, autoimmune, or paraneoplastic etiologies are suspected. If an underlying cause of SFN can be determined, optimal treatment of the causative condition may lessen the symptoms of SFN. Few studies and no guidelines have examined the pharmacologic treatment of the pain associated with SFN. In one such study, both gabapentin and tramadol were found to be effective for SFN. Tricyclics, IV lidocaine, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and intravenous immunoglobulin have all been used.

Rheumatologic

The most common cause of CPP because of a rheumatologic process is PMR, but it is important to note that rheumatologic disease is not as common a cause of CPP as other conditions. Nevertheless, if a rheumatologic condition affects the joints in the pelvic girdle (e.g. inflammatory arthritis), it can manifest as pelvic pain. Out of these, the sacroiliac joint is one of the most commonly affected. The most prevalent disorders associated with inflammatory arthritis are rheumatoid arthritis, ankylosing spondylitis, and gouty arthritis.[108] Systemic lupus erythematosus, myopathy, and osteomalacia are other examples. Rheumatoid arthritis (RA) can cause pelvic pain if it directly affects joints in the pelvis or the bones that make up the pelvic girdle. Some cases of mutilating type of RA have been involved in the development of insufficiency fractures of the pelvic ring, manifesting as progressively worsening pelvic pain.[109,110] RA has also been found to have an association with bladder pain syndrome/interstitial cystitis.[111] Ankylosing spondylitis (AS) is characterized by inflammatory back pain (typically associated with improvement with exercise, insidious onset, nocturnal symptoms, no improvement with rest, and morning stiffness >30 min). Pelvic joint lesions have been reported to be present in about 25%–35% of all patients with AS,

with the severity of hip involvement being correlating to the overall functional status.[112] Gout, on the other hand, is an extremely rare cause of pelvic pain, as fewer than ten cases of gout affecting the pubic symphysis have been reported.[113,114] Treatment of pelvic pain in rheumatologic diseases is directed at treating the underlying condition. NSAIDs, disease modifying anti-rheumatic drugs (DMARDs, e.g. methotrexate), and TNF-inhibitors are the mainstay of treatment in these diseases. Other medications such as colchicine or glucocorticoids in gout can also be considered. Last, there is a significant overlap of CPP and fibromyalgia to the extent that pelvic pain is part of the diagnostic criteria. The levator muscles may benefit from pelvic floor physical therapy and, because of potentiators of muscle tension and trigger points, training with a wand to self-treat at home.

Special Considerations

Children and Adolescents

Special considerations should be taken when evaluating pelvic pain in children and adolescents. As with adults, pelvic pain may stem from gastrointestinal, genitourinary, reproductive, orthopedic, neurologic, congenital, traumatic, or infectious sources, emphasizing the need to take a thorough history to include bowel function, athletic injury, fall, and menstruation. Sensitive questions must be addressed, including inquiry regarding inappropriate touching and other non-consensual physical exposures. This may require the clinician to ask parents and guardians to recuse themselves for part of the patient interview. A female escort must be present for this part of the interview and the physical exam. Examination of the genitals and perianal tissue may be indicated in addition to the neurologic exam, depending on the patient's comfort level and the thoroughness of prior exams within other specialties. A urinalysis should be performed routinely, with cultures, labs, and imaging as indicated. Adolescent males typically only experience pelvic pain after puberty. It is most commonly because of urologic or injuries to the coccyx, genitals (e.g. straddle, zipper, or sexually transmitted disease), or hips. The most common causes of pelvic pain in adolescent females are painful menstruation and constipation, with symptoms often including bloating, nausea, and heartburn. A physician should evaluate significant menstrual pain, and when a young female misses a period three months in a row, periods occur fewer than three weeks apart, or there is frequent bleeding between periods at any point from the initiation of menstruation.[115] A transabdominal pelvic ultrasound may be required, but internal vaginal exams are not typically necessary in children and adolescents. Occasionally a cotton swab may need to be placed into the vagina to test for obstruction or infection. About 70% of adolescent females with pelvic pain are diagnosed with endometriosis.[116] Recommended treatment for endometriosis in adolescents is conservative surgical therapy for diagnosis and treatment, along with continuous suppressive hormonal therapy (i.e. an oral contraceptive) to prevent endometrial proliferation.[117] Because endometriosis implants in adolescents can be difficult to identify as they typically appear clear or red, it is important to refer patients to gynecologists familiar with adolescent endometriosis.

Both male and female adolescents may have myofascial pain from a primary injury or secondary to a known pelvic disorder. Muscles may spasm and become tender to touch, and pelvic floor dysfunction can cause pain with urination or bowel movement. Unlike adults, myofascial pelvic pain in adolescents is not usually associated with local nerve irritation or nerve entrapment, and though a diagnostic nerve block can help differentiate pain from the abdominal wall, spine, and pelvic muscles from other sources, about 95% of adolescent myofascial pelvic pain improves with physical therapy.[118] In adults, pelvic floor physical therapy often involves the vaginal wall, but in adolescents, great benefit can still be derived from indirect stimulation from the external abdominal, hip, thigh, and lower back muscles. Treating chronic pain in adolescents is often easier than in adults because of neuroplasticity. It is often best to address pelvic pain in children and adolescents as a multi-disciplinary team, including pediatricians, adolescent gynecologists, urologists, gastrointestinal medicine doctors, pediatric pain physicians, physical and occupational therapists, and child and adolescent psychologists.

Pelvic Pain in Those With Disability

Patients with intellectual disability (ID) might pose a challenge when managing chronic pain because of communication difficulties, unconstructive behavior, and preexisting conditions complicating diagnosis. Note should be taken of patients' individual circumstances, as every patient with a disability may have different resources, coping skills, and mechanisms.[119] Prevalence of chronic pain has been estimated to be close to 15% in patients suffering from ID. With the understanding that persons with a disability might not be able to communicate distress as effectively, this figure could potentially be higher.[120] Self-reporting is considered the gold standard for assessing pain and should be considered whenever possible. Patients with ID have found some success when it comes to self-reporting and often need the aid of scales such as the visual analog scale. Behavioral observation methods with the aid of observational pain assessment tools have proven beneficial when the patient cannot self-report pain. Tools such as the non-communicating children's pain checklist or the faces, legs, activity, cry, and consolability scale consider several non-verbal cues that provide valuable information about whether pain is present. Management of these patients must include cognitive behavior therapy (CBT) or relaxation therapy in conjunction with medical treatment and teaching family members to identify when a patient is in pain. Coping strategies should be tailored and taught to the needs of each patient, all while giving preference to active coping methods (e.g. functioning despite pain) rather than passive ones (e.g. avoiding the development of pain).[5,121]

Pelvic pain in those with a physical and neurologic disability may best be served by a team including pain management, physical medicine and rehabilitation, neurology, physical therapy, and occupational therapy expertise. Sensory deficits can lead to prolongation of noxious stimulus, for example, prolonged sitting on the coccyx in a wheelchair. In ambulatory individuals, the provider should be cognizant of gait deviations, pain, and weaknesses that can lead to biomechanical compensation. Therapeutic exercise and adaptive equipment applied appropriately can reduce these strains.

Psychological Considerations

People experiencing CPP should be assessed for psychological comorbidities and offered support. It is very important to emphasize that treating the impact of the pain on one's life, psychological amplifiers of pain, and treating the whole person, is important to a good outcome, but that the pain is not thought to be because of a psychological disorder. Most female patients presenting to the clinic experience moderate to severe anxiety, and around 25% have reported moderate to severe depression.[122] These comorbidities,

along with the catastrophizing of pain, can complicate treatment if severe.[5] Relationships and sexual function might also be affected by pelvic pain. Anticipatory anxiety or pain during intercourse can reduce sexual satisfaction and interest. This can lead to concerns about becoming less attractive to existing and new partners.[123] Also of concern is the possibility of past trauma such as sexual abuse or other nonconsensual sexual activities. It has been documented that adolescent girls with a history of sexual abuse are almost twice as likely to report CPP development.[124] A history of trauma is not uncommon in male patients. In all genders, including transgender individuals, a trauma informed approach making room for, but not requesting disclosure of past events while placing the locus of control in the patient's hands usually leads to an easy clinical interaction for all parties involved. CBT and mindfulness-based therapy have both shown success in the treatment of CPP.

Chronification of Pain (Central and Peripheral Sensitization of Pain)

We have discussed some of the central and peripheral neurologic causes of CPP, but it is important to understand that many patients with chronic pain have undergone changes in their neurophysiology. Chronification of pain refers to the transformation of acute pain into chronic pain. It involves the sensitization of peripheral and central nervous systems.[124] The transmission of pain from a nociceptor to the cerebral cortex involves signal transduction, action potential generation, and its transmission to the thalamus and posteriorly to the parietal cortex.[125] Changes within this pathway induce sensitization to pain stimuli (hyperalgesia).

Nociceptors are chemoreceptors that react to inflammatory molecules (bradykinin, prostaglandins, and substance P). Repeated stimulation in the peripheral nervous system results in the upregulation of nociceptors and an increase in neuronal excitability (e.g. by upregulating sodium channels). Second and third order neurons transmit the pain signals to the thalamus and the cerebral cortex, respectively. Central sensitization occurs when these neurons lower the threshold for their action potentials and end up reacting to subthreshold stimuli. The aforementioned sensitization occurs because of an upregulation of N-methyl-D-aspartate receptors, glutamate, and substance P interaction with membrane G-coupled-receptors, and a decrease in γ-aminobutyric acid inhibitory signals.[124]

There are different etiologies of acute-to-chronic pain syndromes. The most common being chronic post-surgical pain (CPSP) and opioid-induced hyperalgesia, with individual patient factors playing a role in the potential for pain chronification. Preexisting conditions or genetic polymorphisms (e.g. mutations in the *COMT* gene) can render an individual more susceptible to developing chronic pain. Obesity, female sex, and young age are also risk factors.[126]

Patients at risk can be preemptively treated with perioperative ketamine, gabapentinoids, NSAIDs, and regional anesthesia. These interventions lower the risk of CPSP.

For the treatment of chronic pain associated with central sensitization, brain-based treatments are centered on re-interpreting messages from the nerves. Interventions can be based on altering memories or fear of pain.[127] TENS units, meditation, relaxation, mindfulness, mind-body medicine, CBT, and exercise can all be beneficial. The provider should focus on reducing any contributing physical pain promotors present (for example, a patient whose pain is complicated by chronic sitting, bladder irritant, and vulvar atrophy).

Employing a multi-disciplinary approach can change how the patient responds to the stimuli, often helping cope with the chronic condition.[128]

Summary

CPP improves or resolves in the majority of patients with a careful, informed, multifaceted approach. The care of these individuals can be very satisfying, and the more knowledge one has, the more effective one will be. Usually, CPP responds to the more straightforward interventions, and the differential diagnosis can be expanded based on the content above where needed.

Key Points

- Pelvic pain can arise from virtually any organ system in the body.
- The approach to acute pelvic pain should rule out life threatening conditions.
- Management of CPP requires a multi-disciplinary team.
- Some serious conditions, such as cancer, might manifest as progressive or refractory CPP.
- Special considerations should be taken when dealing with pediatric patients and patients with disabilities.
- History taking and physical examination should be performed with care because of the nature of the condition.

Acknowledgments

We thank the authors of *Facing Pelvic Pain* for expanding our knowledge in the treatment of pelvic pain enough to write this chapter and to Kenneth Barron, MD, for his suggestions on the gynecologic pain section.

Suggested Readings

European Association of Urology EAU Guideline. Available at: http://www.uroweb.org/guidelines/online-guidelines/.

International Pelvic Pain Society. Available at: https://www.pelvicpain.org/.

ICS Institute. School of pelvic pain. Available at: https://www.ics.org/institute/pelvicpain.

American Urological Association AUA Guideline. Available at: https://www.auanet.org/guidelines/interstitial-cystitis-(ic/bps)-guideline.

The International Continence Society ICS Standardization. Available at: https://www.ics.org/folder/standardisation/current-ics-standardisations.

Levine T, Saperstein D, Argoff C, et al. Small nerves big problems: a comprehensive guide to small fiber neuropathy. Chicago, IL: Hilton Press, 2017.

Patient Resources

De EJB, Stern TA (eds). Facing pelvic pain: a guide for patients and their family members. Boston MA: Massachusetts General Hospital Psychiatry Academy; 2021. Available at: www.facingpelvicpain.org.

Interstitial Cystitis Network. Available at: https://www.ic-network.com/.

World Federation of Incontinent Patients. Available at: https://wfip.org/.

The references for this chapter can be found at ExpertConsult.com.

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Pediatric Chronic Pain Management

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Chronic pain is a significant yet underreported problem in the pediatric population, with a prevalence of up to 25%–45%.[1] It has psychological, emotional, and social implications for both the child and the family.[2] Common pain related functional issues include sleep problems, inability to pursue hobbies, eating difficulties, school absence, and inability to interact with friends.[1] The potential for such consequences to negatively impact a child's quality of life has fostered the development of a multi-disciplinary approach to treat pediatric pain.[3,4] A variety of behavioral, pharmacologic, and physical therapies are employed in pediatric chronic pain treatment regimens. Interventional procedures may be introduced after patients fail other treatment approaches.[5] In this chapter, we discuss common chronic pain syndromes in children, along with their assessment, diagnosis, and management (Box 43.1).

Assessment of Chronic Pain in Children

Assessment of children with chronic pain requires a biopsychosocial framework. Multidimensional models focus on various biologic, developmental, behavioral, affective, sociocultural, and situational factors that contribute to pain severity and the course to recovery.[6,7] Each domain may become a target of assessment and intervention. Several developmentally sensitive validated instruments are now available to measure various aspects of children's pain (Table 43.1).

Two standardized interviews for school-age and adolescent children and their parents provided comprehensive yet practical evaluations of the child's chronic pain: the Children's Comprehensive Pain Questionnaire (CCPQ)[8] and the Varni-Thompson Pediatric Pain Questionnaire. These interviews separately assess both the child's and parents' experiences of pain problems with open-ended questions, checklists, and quantitative pain rating scales. Some studies suggest potential limitations of these self-report measures because of cultural or cognitive differences among children.[9] Additionally, the Pain Behavior Observation Method is a 10 minute observational pain behavior measure that can be used in children with chronic pain who may have difficulty with self-report measures because of age or cognitive limitations.[10] Studies have supported the use of electronic versus paper pain diaries in children with chronic pain; electronic diary use was shown to be feasible and resulted in greater compliance and accuracy in diary recording than did traditional paper diaries in children with recurrent pain.[11]

The well documented comorbidity between pediatric chronic pain and psychiatric disorders,[12] particularly internalizing disorders such as depression and anxiety,[13] obligates the clinician to screen for these disorders. The Children's Depression Inventory (CDI)[14] is a widely used self-report questionnaire for assessing depression in children aged seven to 17 years. It is important to assess anxiety symptoms because pain related disability is associated with anxiety sensitivity, a stable predisposition to fear of anxiety related sensations,[15] and pain related avoidance behavior in children as well as adults with chronic pain.[16] The Children's Anxiety Sensitivity Index (CASI)[15] is the only instrument developed to assess this characteristic in children.

Several well validated self-report questionnaires assessed anxiety in children (see Table 43.1). Two instruments, the Self-Report for Child Anxiety Related Disorders (SCARED)[17] and the Spence Children's Anxiety Scale (SCAS),[18] include subscales that distinguish among specific anxiety disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). The Multidimensional Anxiety Scale for Children (MASC)[19] and the Revised Children's Manifest Anxiety Scale (RCMAS)[20] include subscales that focus on other dimensions of anxiety. These subscales include physical symptoms, social and separation anxiety, and harm avoidance (the MASC) and physiologic symptoms, worry and oversensitivity, and concentration factors (the RCMAS), as well as social desirability items to detect inconsistency or randomness in reporting. The SCAS and SCARED provide both child and parent forms of the instrument, which allows examination of the convergence, or lack thereof, of the child's and parents' assessment of the child's anxiety symptoms.

Factors that are closely linked with a child's ability to function with chronic pain, such as perceived stress[21] and coping,[22] can assist in planning behavioral interventions. The pain coping questionnaire (PCQ),[23] pain response inventory (PRI),[24] and pain catastrophizing scale for children (PCS-C)[25] assess pain specific coping strategies. The identification and modification of maladaptive coping responses constitute the core elements of cognitive behavioral approaches for treating pediatric chronic pain.

The ability to function in tasks of daily living is a critically important outcome measure to assess when treating children and adolescents with chronic pain. Frequently, pain cannot be completely relieved, and the child must learn to accept, cope, and adapt to the pain to enable participation in normal developmental activities and tasks, such as going to school, participating in extracurricular activities, and developing and sustaining social relationships. Several measures have been developed to assess a child's functional abilities and quality of life. For example, the Pediatric Migraine Disability Scale (PedMIDAS) measures headache-related disability in children with chronic pain.[26] This six-question tool assesses school, recreational, and social areas of participation and disability, domains relevant to all children with

• Box 43.1 Chronic Pain in Children: Common Diagnoses

- Neuropathic pain
  - Complex regional pain syndrome type 1
  - Peripheral nerve injuries
  - Postamputation pain
  - Deafferentation pain
- Headache
- Chest pain
- Chronic illness
  - Sickle cell crisis
  - Cystic fibrosis
  - Collagen vascular disease (e.g. juvenile rheumatoid arthritis, systemic lupus erythematosus)
- Recurrent abdominal pain
- Juvenile primary fibromyalgia
- Pelvic pain
- Back pain
- Cancer-related pain

chronic pain. The Child Activity Limitations Interview (CALI)[27] assesses the impact of recurrent pain on children's daily activities as a way to identify appropriate targets for treatment. Additionally, the Functional Disability Inventory (FDI),[28] developed to assess illness-related disability in children and adolescents, is a useful tool for evaluating the functional status of pediatric patients with chronic pain, a particularly important concern in children with pain disorders associated with psychological factors and pain associated disability syndrome.[29] Pain related disability increases with age, and sex differences emerge in adolescence, with more girls than boys reporting pain related functional disability.[30]

Quality of life can also be assessed in children and adolescents with chronic pain and as an index of treatment progress. One study found that the quality of life of children with recurrent headaches is similar to that of children with rheumatoid arthritis or cancer.[31] The Child Health Questionnaire, including both children (CHQ-CF87) and parent reports (CHQ-50),[32] and the PedsQL[33] are measures that may be used to assess the general quality of life in children with chronic pain and have the advantage that the scores obtained on these instruments can be compared with standardized samples of scores obtained by children with other medical illnesses.

Other instruments that may further elucidate the psychological factors contributing to a child's behavioral adaptation to chronic pain include the Children's Somatization Inventory (CSI),[34] which measures a child's propensity to somatization, and the Harter Scales of Perceived Competence,[35] which assesses a child's judgment about his or her capabilities in important domains such as school performance, peer relationships, and athletic abilities. The child's own judgment of his or her competencies in these domains is useful in understanding other factors that may contribute to

TABLE 43.1 Methods for Assessment of Chronic Pain in Children and Adolescents

Pain Measure	Disability or Quality of Life	Stress and Coping	Anxiety	Depression	Other Behavioral Measures
Varni-Thompson Pediatric Pain Questionnaire (PPQ) Ages: 5–18	Functional Disability Inventory (FDI) Ages: 8–17 (plus parent form)	Children's Hassles Scale (CHS) Ages: 8–17	Multidimensional Anxiety Scale for Children (MASC) Ages: 8–19	Children's Depression Inventory (CDI) Ages: 7–17	Children's Somatization Inventory (CSI) Ages: 8–18 (plus parent form)
Children's Comprehensive Pain Questionnaire (CCPQ) Ages: 5–19	Child Health Questionnaire (CHQ) Ages: 5+ (plus parent form)	Pain Coping Questionnaire (PCQ) Ages: 8–18	Self-Report for Childhood Anxiety Related Disorders (SCARED) Ages: 9–18 (plus parent form)	Beck Depression Inventory-II Ages: 13+	Harter Scales of Perceived Competence for Children Ages: 4–12
Pain diary (written, electronic) Ages: 8+	Pediatric Quality of Life Inventory Generic Core Scales (PedsQL 4.0) Ages: 5–18 (plus parent report ages 2–18)	Pain Response Inventory (PRI) Ages: 8–19	Spence Children's Anxiety Scale (SCAS) Ages: 8–12 (plus parent form)		
Pain Behavior Observation Method Ages: 6–17	Pediatric Migraine Disability Assessment Scale (PedMIDAS) Ages: 6–18	Pain Catastrophizing Scale (PCS) Ages: 8-16	Revised Children's Manifest Anxiety Scale (RCMAS) Ages: 6–19		
Non-Communicating Children's Pain Checklist (NCCPC-R) Ages: 2 years old to adult	Children's Activity Limitations Scale (CALI) Ages: 8–16		State-Trait Anxiety Scale for Children (STAIC) Ages: 9–12		
			Childhood Anxiety Sensitivity Index (CASI) Ages: 7–12		

the child's functioning.[36] For example, children with chronic pain who rate themselves as low on social and academic competency may have multiple reasons to avoid returning to school.

A thorough assessment of a child's baseline status and progress is essential to guide interventions for chronic pain and evaluate the response to treatment. The core elements of assessment include a comprehensive evaluation of the child's pain problem and screening for psychiatric comorbidity and functional status (Box 43.2). More intensive screening of the child's perceived stress and competencies and the parents' and family's functioning adds valuable information to treatment planning, especially in a child with long-standing pain problems who has not responded to previous treatment efforts.

Psychological Pain Management Methods

A rehabilitative approach that emphasizes improving the child's and family's ability to cope with a chronic condition characterizes the course of most chronic pain treatment programs for children. The focus shifts from the narrow goal of pain reduction, which might be used in the treatment of acute pain, and broadens to decrease pain related emotional and behavioral disability, thereby increasing the child's functional status.[29,37] Research on the use of psychological therapies has focused mostly on clinical trials in children with headache.[38,39] In a meta-analysis conducted to evaluate the efficacy of behavioral interventions for pediatric chronic pain, Eccleston et al.[40] concluded "There is strong evidence that psychological treatment, primarily relaxation and cognitive behavioral therapy, are highly effective in reducing the severity and frequency of chronic pain in children and adolescents." Additionally, findings by Logan et al. suggest that interdisciplinary pediatric pain rehabilitation may facilitate increased willingness to self-manage pain, which is associated with improvements in function and psychological wellbeing.[39] Finally, promising psychological treatments have also been used for children with disease-related chronic pain, including sickle cell disease,[41] recurrent abdominal pain,[42] complex regional pain syndrome (CRPS) type 1,[43] musculoskeletal pain,[44] and juvenile primary fibromyalgia syndrome,[45] and further support the probable efficacy of psychological approaches to pediatric pain management.

These evidence-based psychological treatment programs are primarily rooted in cognitive behavior therapy (CBT) principles. Traditional CBT and more recent and emerging CBT variations, such as acceptance and commitment therapy, include a diverse array of standard intervention components that treat chronic pain by modifying children's cognitive, affective, and sensory experiences of pain, their behavior in response to pain, and environmental and social factors that influence the pain experience. Education about chronic pain and problem solving for improving the child's functional status is central to the child and family, assuming an active role in managing chronic pain. Cognitive techniques are targeted at modifying the child's thoughts about the pain, in particular, to increase a sense of predictability and control over the pain, to alter memories about painful experiences,[46] and to reduce negative cognitions about pain, notably catastrophizing.[47] Decreasing somatic preoccupation, pain related rumination,[37] and passive coping and learning to accept that the pain may persist are also key interventional goals in the psychological management of pain.[48] Please see Table 43.2 for sample components of CBT in the treatment of pediatric chronic pain.

• Box 43.2 Pediatric Questionnaire Components

1. Developmental level
2. Understanding of pain
3. Pain and medical treatment history
4. Interactions with others in relation to pain
5. Affect and behavior
6. Impact of pain on functional abilities
7. Family environment and stress
8. Coping skills
9. History of psychiatric illness
10. Medical problems

Techniques to alter the sensory aspects of chronic pain include relaxation training, biofeedback, imagery, and hypnosis. Interventions aimed at modifying situational factors that exacerbate chronic pain and disability include contingency or behavioral management methods, modification of activity and rest cycles to achieve a steady pace of activity, and a gradual, structured plan for exposing patients and families to situations previously avoided because of pain.[37,48] Few analyses have been conducted to determine which components of psychological therapies may be essential in the management of pediatric chronic pain, but it is likely that for most chronic pain conditions, a combination of modalities will provide the best opportunity to affect the desired change. Changes in the emphasis of various behavioral components may present an opportunity to individualize treatment for a specific child by taking into account developmental, psychological, parental, and family factors, which may provide a way to tailor specific treatment to a child.

There is growing acknowledgment of parents' crucial role in the successful rehabilitation of children with chronic pain, and thus they are increasingly becoming included as active partners in their child's treatment.[49] Parental interactions with their child related to pain and the family characteristics of children with chronic pain that may be associated with the development of maladaptive coping with pain are areas of active research.[50,51] Particular types of parental behaviors have been shown to influence a child's ability to cope with pain. Walker et al.[51] found that girls with functional abdominal pain are more vulnerable than boys to the symptom-reinforcing effects of parental attention. Interestingly, although the children with pain rated parental distraction as a helpful strategy, their parents rated distraction as having greater potential for a negative impact on their child than attention. Such findings help guide behavioral interventions for children with chronic pain and their families because parents' beliefs in the most effective pain management strategies need to be targeted in any intervention designed to increase the functional abilities of children with chronic pain.

Several methods for the delivery of psychological interventions for recurrent or chronic pain in children have been shown to be effective, including those that involve intensive inpatient or outpatient treatment; those that are self-administered,[52] school-based,[53] Internet-based,[54,55] CD ROM-based[56]; and those that involve minimal clinic contact with home-based practice.[55] The variety of methods for the delivery of these interventions offers opportunities to reach a broad population of children with chronic pain, thus increasing the potential to reach many more children than can be treated in specialized pediatric pain treatment centers. Optimally, the child's school and other caretakers are included in the treatment team to ensure a consistent and comprehensive approach to the child's pain and disability.

The complex nature of chronic pain in children creates many challenges with regard to its assessment and treatment, but this

TABLE 43.2 Sample Components of Cognitive Behavioral Therapy for Pediatric Chronic Pain Treatment

Treatment Domain	Intervention Aims	Intervention Examples
Psychoeducation	• Enhance health literacy • Create positive treatment expectations and optimism for change	• Engaging didactic instruction on basic neuroscience of pain • Analogies describing how chronic pain operates as a faulty alarm and psychological treatments re-set pain signaling in the brain and body
Relaxation Practices	• Activate parasympathetic nervous system • Reduce emotional distress • Enhance self-efficacy	• Diaphragmatic breathing • Progressive muscle relaxation • Guided imagery
Cognitive Skills	• Increase awareness of cognitive patterns • Adopt adaptive thinking patterns • Neutralize affective response to thoughts	• Thought record and detective thinking for self-monitoring of thought-emotion-pain-action patterns • Didactic instruction on cognitive distortions and thinking traps • Cognitive reframing and positive reappraisal practices • Cognitive defusion practices
Behavior Change Skills	• Promote adaptive physical activity • Increase daily developmentally adaptive daily activities • Enhance healthy behaviors	• Graduated exposure to experiences and environments associated with pain exacerbation and distress • Structured physical activity pacing and behavioral activation strategies • Graduated improvements to diet and eating behaviors • Graduated implementation of behavioral sleep medicine principles to decrease nighttime cognitive arousal
Family-focused Skills	• Enhance general family functioning • Promote adaptive parent responses to pain • Improve family communication patterns	• Operant strategies for rewarding adaptive behavior changes • Promote parent and family modeling of adaptive coping with pain and distress • Communication strategies • Structured problem solving skills training

complexity can be exploited to provide the most efficacious methods for pain control and functional rehabilitation. Multidimensional assessment provides the foundation for optimal pain management and functional rehabilitation of chronic pain in children. Psychological interventions include a diverse array of techniques that treat chronic pain by modifying children's cognitive, affective, and sensory experiences of pain, their behavior in response to pain, and environmental and interactional factors that influence the pain experience. Medical treatment of a child's chronic pain may result in poorer outcomes without addressing the psychobehavioral factors that may contribute to pain and pain related disability. Research informed by multidimensional models of pediatric chronic pain can guide investigators in efforts to identify effective pain treatments, as well as the children for whom they work best.

Integrative Medicine Techniques

It has been reported that nearly 75% of pediatric patients, particularly those with chronic health disorders, have used some form of complementary and alternative medicine.[57] A few of the tenets of integrative medicine (IM) include an emphasis on preventative health and lifestyle as well as a consideration of all dimensions of health, including body, mind, and spirit. These concepts make this field a promising adjunct for the treatment of pediatric chronic pain. Data regarding the implementation of IM in pediatric pain practice are limited to headache management and irritable bowel syndrome/functional abdominal pain syndrome. Despite this, a recent study found that it was common for pediatric pain clinics to provide IM, including acupuncture, mind-body therapies, massage, aromatherapy, nutrition counseling, and/or art/music therapy.[58] We frequently recommend these therapies to our patients, as well as other techniques such as vitamin supplements/herbal remedies, chiropractic manipulation, and biofeedback.

Chronic Pain Syndromes

We will briefly discuss the diagnosis and management of some common chronic pain syndromes diagnosed in pediatric patients referred to chronic pain clinics. The introduction of multidisciplinary pediatric pain clinics has allowed children to be seen in a single office visit by several consultants who can provide services for the child and develop a comprehensive pain management plan. An example of this model includes an anesthesiologist specializing in pain management, a pediatric pain psychologist, a physical therapist, a complementary medicine practitioner (including massage therapy and acupuncture therapy), and a specialist in biofeedback. This comprehensive approach reduces the need for multiple visits and exposes patients to a multimodal therapeutic approach.

Common pain syndromes in children include CRPS type I, headache, abdominal pain, juvenile primary fibromyalgia, chest wall pain, back pain, pelvic pain, and cancer-related pain. We address each of these conditions with a specific emphasis on accepted current therapy.

Complex Regional Pain Syndrome

CRPS type I or reflex sympathetic dystrophy (RSD), as originally named, is a complex syndrome consisting of neuropathic pain symptoms including allodynia and hyperalgesia, sudomotor dysfunction, and motor/trophic changes. In the pediatric population, it occurs more commonly in the lower extremity,[59] with a female preponderance.[60] Significant trauma is found with less frequency than in the adult population.[60] Though there is a case report

involving a two and half-year-old girl,[61] it is generally seen in children older than nine years and more frequently in adolescents 11–13 years of age.[62] Compared to adults, children are thought to better respond to non-invasive and treatment strategies and have a more favorable prognosis with treatment.[43] However, early recognition and management are the major factors in improving outcomes and preventing resistant CRPS.[63] Data regarding the epidemiology of CRPS type I is limited, though case reports exist describing pain in the sciatic distribution patients as young as three years old.[64,65]

Evaluation of Complex Regional Pain Syndrome I

History

A detailed history of the nature of the injury, the type and duration of the pain, relieving and aggravating factors, and dependence on medications is mandatory before evaluation.

Physical Evaluation

Thorough and systematic neurologic examination should be performed. Complete evaluation of the motor, sensory, cerebellar, cranial nerve, reflex, cognitive, and emotional functioning should be conducted. A concerted effort must be made to rule out a rare but possible malignancy or central degenerative disorder that may include laboratory evaluation, imaging such as X-rays, magnetic resonance imaging (MRI), or computed tomography (CT), or electromyography of the affected limb.

The strength of the extremities should be evaluated on several occasions. It is important to compare it with the strength in the contralateral extremity because CRPS I can occur in both extremities at the same time. Allodynia, pain to a stimulus that is not typically painful, is a common finding. Hyperalgesia, an increased painful response, is also common, particularly to cold sensation.[66] Similarly, in adults, distribution is not generally restricted to particular dermatomes and commonly occurs along a glove-and-stocking distribution. Although nerve conduction studies may provide insight into a specific nerve injury, sensory abnormalities appear in different combinations in patients despite similar clinical presentations pointing to a central origin of pathogenesis.[67] Quantitative sensory testing (QST) with thermal and vibration sensations and thermal pain detection thresholds in the affected limbs can be compared with data from normal healthy children. Although this involves cumbersome equipment, bedside QST may play a greater role in the diagnosis of CRPS I in children and adolescents.[68] Bone scans may be helpful in the diagnosis of CRPS. However, there is limited data on their diagnostic accuracy in children. A decrease in isotope uptake was observed with suspected CRPS I.

Diagnosis

The diagnosis of CRPS I in children was based on symptoms and signs (Table 43.3). The characteristics of pain and sensory, motor, and sudomotor changes may vary among patients. The 1994 International Association for the Study of Pain (IASP) criteria for CRPS I and the 2003 Budapest criteria can be applied to children and adolescents (see Box 43.3a and 43.3b). However, it should be noted that although the Budapest criteria have been found to have nearly 100% sensitivity and 70%–80% specificity in the adult population, these criteria have not been validated in the pediatric population.

Treatment of CRPS I. Treatment of CRPS should be immediate and directed toward restoration of extremity function and rehabilitation.[69] Management of CRPS (Box 43.4) can be frustrating for the caregiver and the patient as no single therapy can uniformly provide relief to these patients. The treatment plan should be multidisciplinary in nature. Although medications can be prescribed and procedure-based treatments may be performed in children, rehabilitative treatments show the best evidence for positive outcomes. Logan et al. studied the effects of an intensive, multi-disciplinary model of daily cognitive behavioral and physical occupation therapies with medical and nursing services for pediatric CRPS over a three week timespan[39] and found that patients experienced significantly decreased pain perception, improved functional ability and limb function, and improved emotional functioning.

One of the primary goals is to return the child to a functional state and school, as a definitive resolution of the pain is not always possible. Most management techniques have been extrapolated from work done in adult patients.[70] It is imperative to build trust with the patient and the parents. Family dynamics are important because the added burden of familial disharmony or parental abuse can worsen the symptoms. There seems to be a greater propensity for enmeshment in these families.

Psychological and Behavioral Therapy

Psychologic therapies are a pillar in the treatment of pediatric CRPS and may require the expertise of a pain psychologist. Although no one therapy has been proven to be the "gold standard," CBT is generally the accepted treatment strategy. Other

TABLE 43.3 Symptoms and Changes in Stages of Chronic Regional Pain Syndrome Type 1

Characteristic	Acute	Dystrophic	Atrophic
Pain	Hyperpathic, burning	Chronic	
Blood flow	Increased	Decreased	No change
Temperature	Increased	Decreased	No change
Hair and nail growth	Increased	Decreased	Chronic change
Sweating	Decreased	Increased	No change
Edema	None	Brawny edema	Wasted muscles, atrophic skin
Color	Red	Cyanotic	Atrophic

• Box 43.3a International Association for the Study of Pain Diagnostic Criteria for Complex Regional Pain Syndrome

1. Presence of an initiating noxious event or cause of immobilization
2. Continuous pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
3. Evidence at some time of edema, changes in blood flow, or abnormal sudomotor activity in the region of pain
4. Diagnosis excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

Adapted from Bruehl S, Harden RN, Galer BS, et al. External validation of the IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria International Association for the Study of Pain. *Pain*. 1999;81:147–154.

• Box 43.3b Budapest Criteria

Budapest Criteria for Complex Regional Pain Syndrome

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of four* of the following categories

Sensory	Reports of hyperesthesia and/or allodynia
Vasomotor	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/edema	Reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least *one sign at time* of evaluation in *two or more* of the following categories

Sensory	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
Vasomotor	Vasomotor: evidence of temperature asymmetry (>0.6°C) and/or skin color changes and/or asymmetry
Sudomotor/edema	Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic	Evidence of a decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms

Reproduced with permission: Harden RN, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. *Pain*. 2010;150(2):268-74.

techniques, including biofeedback, visual guided imagery, and structured counseling, have been shown to assist in the development of adequate coping skills.[71] Participation in a day program for acute psychological intervention has been valuable for some of our patients, specifically those with significant psychiatric co-illness. More detailed explanations of the various psychological interventions have been provided in a previous section.

Physical Therapy

Physical therapy is geared toward the adequate functional ability of the child. Transcutaneous electrical nerve stimulation (TENS) is widely used, and its efficacy has been studied in adults and children. The therapeutic benefits of TENS in children with RSD have been reported by Kesler et al.,[72] who used TENS regularly in their practice, along with physical therapy, which consists of both active and passive physical modalities. The physical therapy program is geared toward individual patients, with the primary goal of maximum participation. It may be necessary to have input from a specialized pediatric physical therapist or occupational therapist for adequate management. Commonly used treatment options for CRPS include desensitization, graduated weight bearing, exercise therapy, graded motor imagery, warm and cold baths, massage therapy, and water emersion therapy.

Medical Therapy

Most medical treatment strategies for children have been extrapolated from adult data. These include pharmacotherapy, regional anesthetics, sympathetic blockade, and neuromodulation. Over counter medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are typically trialed by patients and families for initial pain treatment. However, there are mixed data regarding their efficacy.[62] Anti-neuropathic pain medications can be trialed sequentially, although toxicities and side effects should be monitored closely in pediatric patients (see Box 43.4).

Tricyclic Anti-depressants. Adults are frequently prescribed tricyclic anti-depressants (TCAs) for the management of NP.[73] Despite the lack of adequately controlled studies in pediatric patients, TCAs are widely prescribed for several forms of NP.[74] Because amitriptyline may cause sedation, it is our practice to use nortriptyline, which appears to have less sedative and fewer anticholinergic side effects. A thorough examination of the cardiovascular system is necessary before instituting TCA treatment because of associated tachydysrhythmia and other conduction abnormalities of the heart, particularly prolonged QT syndrome.[75,76]

Anti-convulsants. Anti-convulsant medications have been used for several years to manage NP.[77] Although carbamazepine and oxcarbazepine have been used extensively to treat NP, the introduction of gabapentin and pregabalin has revolutionized the world of pain medicine.[78–80] Despite the lack of controlled trials in children to demonstrate the efficacy of either drug, both of these voltage-gated calcium channel blockers have been used in our clinic with promising results. More controlled trials are needed to better determine the dosing and efficacy of this class of drugs in children with CRPS 1.[80] An important side effect that we have noted in our clinic setting is the potential for increased somnolence and the potential for weight gain. Similar to other anti-convulsant medications, there are concerns regarding mood changes and increased agitation and aggression in adolescents taking gabapentinoids. As such, the Food and Drug Administration

• Box 43.4 Management of Neuropathic Pain

1. Nonpharmacologic Treatment
   - Hypnosis, biofeedback, visual guided imagery
   - TENS, physical therapy, occupational therapy
   - Individual and family therapy (day program if required)
2. Pharmacologic Therapy
   - Acetaminophen, NSAIDs
   - Tricyclic anti-depressants (e.g. amitriptyline, nortriptyline, doxepin); start at low doses, 0.1 mg/kg, and advance slowly
   - Anti-convulsants (gabapentin, pregabalin, carbamazepine, phenytoin, and clonazepam), systemic local anesthetics (mexiletine, lidocaine)
   - Serotonin and norepinephrine reuptake inhibitors
   - Opioids (morphine, methadone administered orally, intravenously, or via a regional technique [epidural or intrathecal], especially in cancer patients)
3. Regional Blockades for Chronic Pain
   - Epidural, subarachnoid and sympathetic plexus, peripheral catheter blockade
   - Sympathetic blockade for CRPS 1
   - Continuous catheter techniques may be used for five to seven days
   - Epidural and subarachnoid block for cancer patients: left in place for longer periods by subcutaneous tunneling
   - Neurolytic blockade for cancer

CRPS, Complex regional pain syndrome; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *TENS*, transcutaneous electrical nerve stimulation.

(FDA) has issued a warning for increased suicidiality[81] with these medications, and families should be counseled prior to initiating therapy.

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors. Despite the lack of proven efficacy of the use of selective serotonin reuptake inhibitors in the management of pain in children and adolescents, they are occasionally used to treat psychological comorbidities, including depression associated with pain.[82] More recently, serotonin-norepinephrine reuptake inhibitors have been successfully used to treat NP, especially in patients with psychological comorbidity.[83]

Systemic Vasodilators. Several patients with RSD have benefited from the use of vasodilators such as prazosin, nifedipine, and phenoxybenzamine. However, the overwhelming adverse effects of orthostatic hypotension often offset the efficacy of this therapy.

Regional Anesthesia and Sympathetic Blocks. A common treatment for these syndromes is to interrupt the apparent pathologic reflexes by performing sympathetic blocks (Box 43.5). Regional anesthesia, although used often in adults for the diagnosis and management of CRPS, is generally introduced in children after pharmacologic, physical therapy, and cognitive behavior management have been exhausted.[5] Recently, Zerkinow et al. synthesized a review of invasive procedures for children between 8 and 15 years of age with complex regional pain syndromes. They found 36 studies with a total of 173 patients who underwent a procedure, and the procedures varied depending on the decade they were performed. Because of the poor quality of the studies and lack of control, the effectiveness of invasive therapies in pediatric CRPS remains uncertain, and further randomized controlled studies are required.[84] In this section, we discuss the different regional techniques that can be useful in children for the management of CRPS.

Central neuraxial blockade is used in children with severe pain to facilitate the introduction of physical therapy. An indwelling epidural catheter is placed in the lumbar or cervical area and infused with a low-concentration local anesthetic solution, which allows better cooperation from the patient and the parents to introduce a physical therapy regimen. In addition, intrathecal analgesia has been reported to be an effective method for treating refractory CRPS 1 in children.[85,86]

Bier block has been used for mild to moderate cases of CRPS 1 as a primary modality for providing analgesia and sympathetic blockade. Although a myriad of substances have been used to provide a Bier block, a local anesthetic in combination with either an α_2-agonist or an NSAID appears to produce better results. In our case series of children who received intravenous regional anesthesia with lidocaine and ketorolac, we demonstrated a marked improvement in symptoms and the ability to perform physical therapy.[70]

• Box 43.5 Regional Anesthesia for Complex Regional Pain Syndrome Type 1

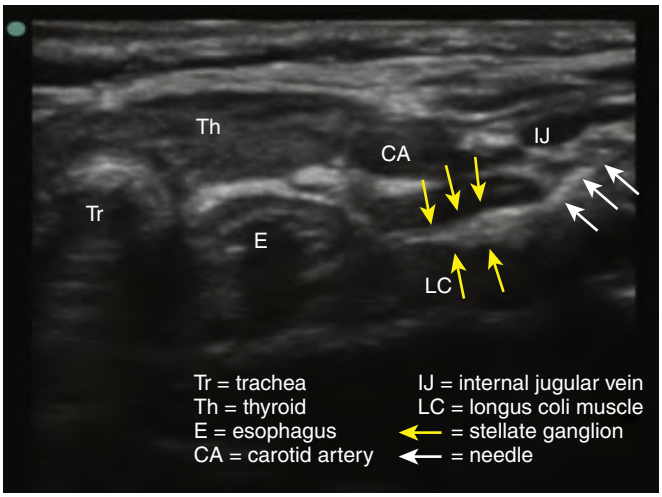
- Intravenous regional anesthesia-guanethidine, bretylium, lidocaine-ketorolac
- Epidural analgesia (continuous)
- Intrathecal analgesia
- Sympathetic chain blocks
  - Stellate ganglion blocks
  - Lumbar sympathetic blocks
- Brachial plexus catheters
- Sciatic nerve catheters

Peripheral nerve blocks are used to facilitate physical therapy while providing a sympathectomy and have become more plausible, especially with the use of ultrasound guidance.[87] Serial peripheral nerve blocks may be performed, which provides pain relief that may outlast the duration of conduction blockade. This may be because of reduced central sensitization, as well as interruption of the circuit established between the nociceptor, central nervous system, and motor unit.[88]

Continuous peripheral nerve blocks (CPNBs) have been reported to be effective in controlling pain and facilitating physical therapy in children with CRPS.[89] Despite such reports, limited data exist regarding the feasibility, safety, and efficacy of CPNBs in children.[90] After perineural catheter placement, a dilute solution of local anesthetic is infused with the view of providing analgesia while allowing physical activity. The catheter is left in place for four to five days; this can be done on an inpatient basis, or the patient may be sent home with a portable infusion device. We prefer sciatic nerve catheter placement for the lower extremities (see Fig. 43.1) and interscalene or infraclavicular brachial plexus catheters for the upper extremities. Concurrent physical therapy is indicated to improve the range of motion and function. We instituted physical therapy at the time of provision of a nerve block to enhance the patient's experience with therapy.

Sympathetic blockade was used in children after exhausting the aforementioned techniques. A stellate ganglion block may be performed under ultrasound guidance for upper extremity CRPS (see Fig. 43.2), and a lumbar sympathetic block is performed

• Figure 43.1 Sciatic nerve catheter for the management of complex regional pain syndrome type 1.



• **Figure 43.2** Image of ultrasound guided stellate ganglion blockade.

under fluoroscopic guidance for lower extremity CRPS.[91] A crossover trial of fluoroscopically guided lumbar sympathetic blocks demonstrated a decrease in allodynia and pain intensity compared with intravenous injection of lidocaine in adolescents with CRPS.[92]

Neuromodulation via spinal cord stimulation, though commonly performed in adults for refractory cases of CRPS, is very rarely used in the pediatric setting.[93] Spinal cord stimulation has been reported to achieve favorable outcomes in adolescents with therapy-resistant CRPS.[94] The use of peripheral nerve stimulators is gaining ground in the pediatric setting and may benefit children with refractory CRPS with a nerve distribution.

Headaches

Headaches are common in children and adolescents. Few physicians discussed headaches in children until 1873, when William Henry Day, a British pediatrician, devoted a chapter to the subject of headaches in his book *Essays on Diseases in* Children.[95] Modern medical literature and the study of pediatric headaches have grown significantly. In 1962, Bille published a landmark study of 9000 children, showing reported migraine headaches in 3.9% of children younger than 12 years and a 6.8% incidence of nonmigrainous headaches daily.[96] Since then, the reported incidence has grown. In a meta-analysis of 27,000 children between 1977 and 1991, it was reported that up to 51% of children experienced a significant headache by the age of 7 years, which gradually increased to nearly 82% by age 15 years.[97]

Most headaches in children are linked to either organic or nonorganic causes and may be deemed acute or chronic based on the duration of the headaches. Chronic daily headache is classified as a headache that occurs at least 15 times monthly for three months and can last for more than 4 hours daily.[98]

Evaluation of Headache

A thorough history and physical examination helped determine the nature of the headache. Specific questions about neurologic symptoms, such as ataxia, lethargy, seizures, and visual impairment, should be asked. Other medical conditions, such as hypertension, sinusitis, and emotional disturbances, must be evaluated. Physical examination, including a thorough neurologic examination and blood pressure measurement, is mandatory for children with headaches. Neuroimaging may be required, and lumbar puncture may be advised in some cases. Benign intracranial hypertension or idiopathic intracranial hypertension is a constellation of symptoms and signs, including headaches, diplopia, tinnitus, and eye pain. These conditions usually have normal imaging results.[99] Although a diagnostic lumbar puncture may be needed in some settings, patients with chronic daily headaches may be prone to post-lumbar puncture headaches.[99]

Pathophysiology of Headache

Headache is modulated by extracranial and intracranial structures (Box 43.6).

Classification of Headache

Classification of headaches is based on the presumed location of the abnormality, its origin, its pathophysiology, or the symptom complex that the patient has (Box 43.7).

• Box 43.6 Pathophysiology of Headache

1. Pain-Sensitive Headache
   - Extracranial
     - Skin
     - Subcutaneous tissue
     - Muscles
     - Mucous membranes
     - Teeth
     - Larger vessels
   - Intracranial
     - Vascular sinuses
     - Larger veins
     - Dura surrounding the veins
     - Dural arteries
     - Arteries at the base of the brain
2. Pain-Insensitive Headache
   - Brain
   - Cranium
   - Most of the dura
   - Ependyma
   - Choroid plexus

• Box 43.7 Classification of Headaches: Differential Diagnosis

Acute headache
- Systemic illness
- Subarachnoid hemorrhage
- Trauma
- Toxins such as lead or carbon monoxide
- Electrolyte imbalances
- Hypertension

Acute recurrent headache
- Migraine
- Tension headache

Chronic progressive headaches
- Organic brain disease
- Ventriculoperitoneal shunt malfunction

Chronic nonprogressive headache
- Functional in quality

Mixed headache

Evaluation of Headache

Comorbid symptoms are associated with headaches. Sleep deprivation is the most common comorbidity. Delayed sleep is a frequent disorder observed in children with headaches. Many also have symptoms of dizziness, which may be associated with postural hypotension and tachycardia (postural orthostatic tachycardia syndrome). Orthostatic hypotension should be treated by increasing fluid intake, and in some cases, a β-blocker may be needed. A history of a new-onset severe headache, pain that awakens a child from sleep, headaches associated with straining, changes in chronic headache patterns, or the presence of a headache accompanied by nausea or vomiting suggests a more pathologic origin of the headache and must be carefully evaluated (Box 43.8).

It is imperative to evaluate any relevant neuroimaging studies before the patient's appointment in the pain clinic. After establishing that the headaches are not secondary to any intracranial pathology, the following information is obtained:

1. Neurologic status, including a complete neurologic examination.
2. Physical/functional status of the patient.
3. Does the headache prevent the child from performing normal activities (e.g. interacting with others and participating in sports)?
4. Is there a history of school absenteeism?
5. What is the child's interaction with the parents and siblings at home?
6. Are there any factors that relieve the headache?
7. Has the child been taking medications for pain? Has there been any improvement in the clinical characteristics of the pain?
8. Are postural changes associated with headaches? Is there a diurnal variation in headaches?
9. Family history is crucial in these children; a family history of migraine is suggestive of childhood migraine.

After careful evaluation and classification of the type of headache, treatment is initiated in a stepwise fashion. An example of an algorithm for the management of headaches is presented in Fig. 43.3.

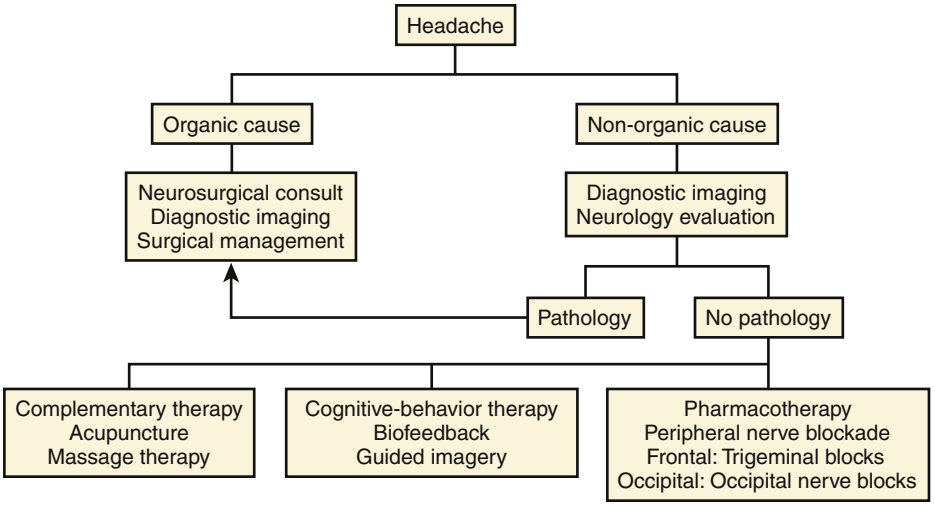
Patients with migraine headaches are frequently managed by neurologists and are referred to the pain clinic only in refractory cases. We have intervened in providing peripheral nerve blocks for headaches. A trigeminal nerve block for frontal headaches and occipital nerve blocks for persistent occipital pain have been shown to be effective in children.[100]

• Box 43.8 Evaluation for Headache

1. General Physical Examination
   - Blood pressure, postural hypotension
   - Careful skin examination for café-au-lait spots, adenoma sebaceum, hypopigmented lesions, petechiae
2. Neurologic Examination
   - Cranial circumference measurement
   - Bruit on auscultation of the cranium
   - Tenderness in the sinuses or presence of occult trauma indicating a battered child
   - Funduscopic examination- optic atrophy, papilledema
   - Cranial nerve examination for the presence of damage
   - Mental status
   - Alteration in language skills
   - Alteration in gait
   - Cranial nerve examination
3. Laboratory Tests
   - Electroencephalography-very non-specific
   - Computed tomography scan, especially with contrast enhancement, may be useful in determining vascular abnormalities.
   - Magnetic resonance imaging- best for delineating abnormalities in the sella turcica, posterior fossa, and temporal lobes
   - Lumbar puncture helpful in determining acute infectious causes
   - Psychological tests to determine whether the headache has a psychological basis
   - Tilt test- if postural hypotension is present (postural orthostatic tachycardia syndrome)
   - Angiography (venous or arterial) if intracranial pathology is suspected.

A tension-type headache is perhaps the most common type of headache that we observed in our pain clinic. These patients frequently complain of debilitating frontotemporal or frontoparietal headaches. Headaches result from contraction of the temporalis muscle and tension on the scalp muscle.[101] Management of tension-type headaches includes the use of relaxation techniques, as well as biofeedback. These patients frequently benefit from the routine use of nonsteroidal agents.[102]

Migraine headaches can be treated with abortive medications such as triptans or with common analgesics, including acetaminophen, aspirin, ibuprofen, naproxen, or opioids such as hydrocodone or tramadol. Medication overuse headache can occur with the



• Figure 43.3 Algorithm for the management of headaches. If the patient experiences nausea, vomiting, or other signs of increased intracranial pressure, neurosurgical consultation should be obtained.

frequent use of these medications and can occur if medication use is more than 10 days per month or more than 15 days per month for a period greater than three months.[103] In these cases, preventative medications should be considered, such as propranolol, amitriptyline, topiramate, or similar medications. OnabotulinumtoxinA and erenumab-aooe are injectable medications that have been approved for the prevention of migraines. However, studies regarding its efficacy in pediatric patients are lacking.[104]

Children occasionally have persistent neuropathic headaches. This commonly occurs in patients who have undergone ventriculoperitoneal shunt revision or surgical decompression for Chiari malformation. After CBT, we attempted to use serial peripheral nerve blocks in these patients. This includes trigeminal nerve blocks for the frontal and occipital nerve blocks for occipital headaches. An ultrasound guided approach to the occipital nerve allows easy access to the C2 nerve root, thereby providing a more robust blockade than can be achieved with a peripheral subcutaneous injection.[105] Local anesthetic is injected with or without a small dose of steroid to provide analgesia.

Juvenile Primary Fibromyalgia Syndrome

Juvenile primary fibromyalgia syndrome (JPFS) is an idiopathic pain syndrome that affects up to 6% of children and adolescents.[106,107] It is a condition characterized by chronic widespread musculoskeletal pain, sleep disturbance, fatigue, and multiple discrete tender points to palpation. Clinical diagnosis is based on history, physical examination, the absence of other pathologic conditions that would explain fatigue and pain, and normal laboratory workup. Other associated symptoms include chronic anxiety, chronic headaches, soft tissue swelling, and pain modulated by physical activity, weather, and emotional stress.[108] There is significant morbidity associated with JPFS, including poor school attendance, difficult physical functioning, poor social acceptance, and comorbid mood disorders.[107] Adolescent patients with JPFS have a high likelihood of continuing symptoms into adulthood.[28] It most frequently affects adolescents between 10 and 15 years of age and has a propensity to affect females more than males.[106]

Diagnosis of Juvenile Primary Fibromyalgia Syndrome

Previously, the diagnosis of JPFS was made using the Yunus and Masi 1985 criteria, including three months of associated fatigue, sleepy difficulty, anxiety, and painful tender points on examination.[107] However, it lacked validation and critical analysis. In 2010, Wolfe et al. proposed criteria for adult fibromyalgia that included the Widespread Pain Index (WPI) and Symptom Severity (SS) Scale for key symptoms of fibromyalgia Table 43.4. This has been found to be an effective screening and diagnostic tool in the adolescent female population with JPFS and is the diagnostic tool utilized in our clinic.

Treatment of Juvenile Primary Fibromyalgia Syndrome

A multi-disciplinary model is the most accepted treatment strategy for JPFS. This includes biobehavioral, pharmacologic, and exercise-based modalities. Psychological therapies, most prominently CBT, have significant evidence demonstrating efficacy in the treatment of JPFS. There is a paucity of data regarding the pharmacologic treatment of JPFS. Various medication classes have been trialed in treating JPFS. However, efficacy data remain limited.[106] As such, pharmacologic treatment strategies are extrapolated from validated adult studies. Tricyclic anti-depressants (TCA), most notably amitriptyline, have been found to be effective in several parameters in adult fibromyalgia syndrome. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have also been tested in JPFS, given the high prevalence of comorbid depression and anxiety. However, the "black box warning" for suicidal ideation in adolescents with a history of major depressive disorder should be considered and monitored with close parental and psychiatric follow up.[109] Opioid antagonists, such as low dose naltrexone, have been actively researched in recent years for the treatment of adult fibromyalgia syndrome. It is hypothesized that low doses of naltrexone, 1–5 mg daily, inhibit glial inflammatory response by Toll-like receptor 4 modulation and systemically upregulate endogenous opioid providing analgesia. In adults, it has been shown to decrease pain and anxiety and improve sleeping habits from baseline after a three month treatment period.[110] Typical doses range from 1–5 mg daily. Despite a lack of studies on its use in pediatric patients, it has a relatively low side effect profile and relative tolerability by patients, making it an ideal adjunct in the treatment of JPFS. Other medications that have been trialed without variable support include gabapentinoids, muscle relaxers, and nonsteroidal anti-inflammatory drugs.

Abdominal Pain

Abdominal pain is a frequently encountered problem in infants, children, and adolescents. When evaluating abdominal pain, it is imperative that all organic causes are eliminated. Abdominal pain may be classified as visceral, parietal, or functional.[111] Functional abdominal pain (FAP) is defined as pain unrelated to an identifiable organic gastrointestinal disorder.[112] Once a diagnosis of FAP is established, CBT along with family centered therapy has proven effective.[113] Several authors have described an affective component of FAP.[114] Furthermore, Walker et al. suggested that children with FAP are at increased risk for the development of chronic pain in adulthood.[115] This may be because of mechanisms linked to heightened central sensitization. Amitriptyline has been described as an effective treatment for FAP in children, although a randomized prospective trial demonstrated no significant difference between control and amitriptyline.[116]

Diagnosis of anterior cutaneous nerve entrapment syndrome (ACNES) is often missed because of the focus on the visceral system as well as misdiagnosis of FAP.[111] However, Siawash et al. found that ACNES was present in 13% of pediatric patients with abdominal pain.[117] Pain can often be superficially localized and described as a stabbing or burning sensation. Given that it is primarily a condition of the abdominal wall, the pain can be aggravated by daily activities such as running or cycling. Commonly, patients show a positive Carnett sign, which involves increased tenderness in painful locations with muscle tension.[117]

Serial nerve blocks in children with abdominal pain, particularly those in whom NP develops after abdominal surgery. The use of serially performed ultrasound guided rectus sheath blocks or transversus abdominis plane blocks has decreased abdominal pain in our cohort as well as in patients with ACNES.[118] By blocking the thoracolumbar nerve roots, analgesia is provided to the anterior abdominal wall (see Fig. 43.4).

Ilioinguinal neuralgia following hernia repair is an underreported cause of abdominal pain in older children and adolescents[119] and is probably secondary to major dissection during surgery. TENS may be helpful, and peripheral nerve blocks can be used to manage pain. Serial ultrasound guided ilioinguinal nerve blocks have been demonstrated to be effective.[120] A perineural catheter may be left in place in severe cases. Implantable peripheral nerve stimulation for inguinal post-surgical neuralgias

TABLE 43.4 Widespread Pain Index (WPI) and Symptom Severity (SS) in the Diagnosis of Fibromyalgia

Widespread Pain Index

A. Have you had pain in the following location in the last week?

Shoulder, right	Shoulder, left	Upper arm, right	Upper arm, left
Lower arm, right	Lower arm, left	Hip (buttock), right	Hip, left buttock
Upper leg, right	Upper, left	Lower leg, right	Lower leg, left
Jaw, right	Jaw, left	Chest	Abdomen
Upper back	Lower back	Neck	

Symptom Severity (SS)

B. How much of a problem have the following been for you during the past week?

	No problem	Slight mild problem, generally mild or intermittent	Moderate, considerable problem, often present	Severe, pervasive, continuous, life disturbing problem
Fatigue	0	1	2	3
Waking still feeling tired	0	1	2	3
Concentration or memory problems	0	1	2	3

C. Have you had problems with any of the following during the past three months?

Muscle pain	Headache	Sun sensitivity	Chest Pain
Muscle weakness	Dizziness	Blurred vision	Hair loss
Numbness/tingling	Shortness of breath	Loss/changes in taste	Fever
Irritable bowl syndrome	Nervousness	Hearing difficulties	Thinking problems
Abdominal pain/cramps	Depression	Ringing in the ears	Dry mouth
Diarrhea	Fatigue/tiredness	Easy bruising	Dry eyes
Constipation	Insomnia	Frequent urination	Itching
Heartburn	Loss of appetite	Bladder spasms	Wheezing
Vomiting	Rash	Painful urination	Oral Ulcers
Nausea	Hives/welts	Seizures	Raynaud's

Part C Score: 0 = No symptoms, 1 = Few symptoms, 2 = Moderate number of symptoms, 3 = Many symptoms

WPI = A Score

SS = B Score + C Score

Fibromyalgia if WPI greater than or equal to 7 and SS greater than or equal to 5 or WPI 3–6 and SS greater than or equal to 9.

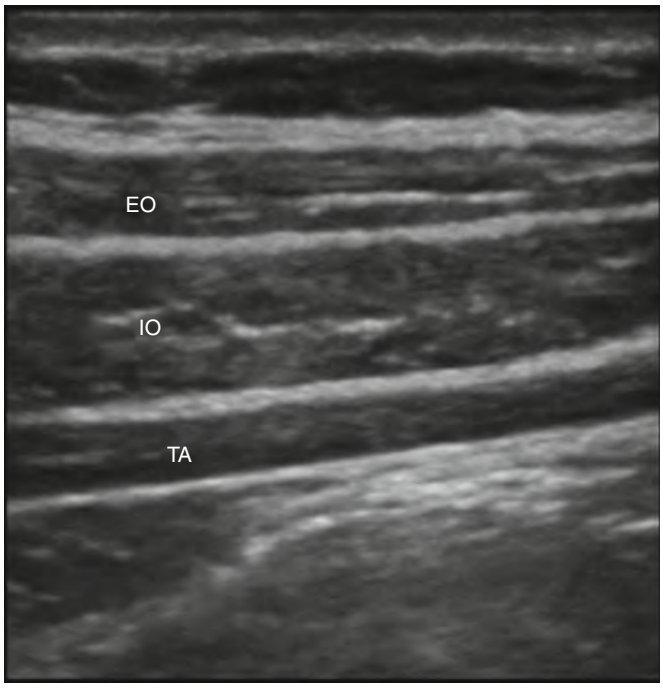
has promising results in the adult population. However, data are limited in pediatrics.[121]

Chest Pain

Chest pain is a common symptom in older children and adolescents. A study conducted in Belgium reported a greater preponderance in men.[122] Most children encountered in the emergency department complained of chest tightness with pain located lateral to the sternum.[123] In a study of 96 patients with a mean age of 13 years, 37% had idiopathic chest pain. A major life event, such as a family divorce or death of a relative, was a significant factor predisposing to chest pain in more than 30% of these children.[124]

Causes of Chest Pain

The most common causes of chest pain include chest wall pain (64.5%), cardiac (5%), respiratory (13%), gastrointestinal (3%), psychological (9%), and traumatic causes (5%). After cardiac causes are ruled out with an electrocardiogram and a careful physical examination, other causes of chest pain should be considered.[124] Each has similar initial symptoms, although the diagnostic workup may be different, depending on the physical findings (Table 43.5).



• **Figure 43.4** Sonographic anatomy of the transversus abdominis (*TA*) plane. *EO*, External oblique muscle; *IO*, internal oblique muscle.

TABLE 43.5 Causes of Chest Pain

Cause	Manifestations
Chest wall pain	Musculoskeletal chest wall pain, costochondritis, Tietze's syndrome
Respiratory disease	Pneumonia, pleuritis, asthma, upper respiratory infection
Psychogenic	Anxiety, depression, hyperventilation
Traumatic	Soft tissue injury, pneumothorax
Cardiac	Carditis, arrhythmia, mitral valve prolapse, ischemia
Digestive	Esophagitis, gastritis
Miscellaneous	Sickle cell disease, cystic fibrosis related

Chest Wall Pain

This is often seen in teenagers and manifests as acute pain along the costal margin. The most common chest wall pain is secondary to costochondritis.[124] The diagnosis is made by eliciting pain along the costochondral margin with deep pressure. Other chest wall pain syndromes include Tietze's syndrome and slipping rib cage syndrome,[125] which usually consists of the use of NSAIDs. We have seen several patients with slipping rib cage syndrome who have not experienced relief despite surgical resection of the slipping rib. We used CBT as well as alternative therapies, including acupuncture and massage therapy, for these children. In addition, we successfully placed intercostal nerve blocks under ultrasound guidance and achieved good relief in children with severe recurring chest wall pain. Serial blocks are performed with adequate resources available for biofeedback and massage therapy to alleviate any pain associated anxiety.

Pulmonary Causes

The most common respiratory emergencies manifesting as acute chest wall pain occur in children with acute asthma attacks, who may have primarily chest pain without concurrent respiratory symptomatology. Other common causes include bronchial pneumonia and respiratory illnesses, including severe lower respiratory tract illnesses. Management includes treating respiratory illness with antibiotics, anticholinergics, and inhaled bronchodilators.

Cardiac Causes

Cardiac causes of chest pain are probably the most compelling reasons for a thorough diagnostic workup. The most common cardiac causes of chest pain include mitral valve prolapse and dysrhythmias. Workup may include echocardiography, electrocardiography, and, in some cases, Holter monitoring for diagnosis. It is important to address pain in an expeditious manner with a close evaluation.

Abdominal Causes

Gastroesophageal reflux is the most common abdominal cause of continued chest pain in children. In addition, the presence of eosinophilic esophagitis should be ruled out by upper endoscopy because it can usually be treated.

Psychogenic Causes

Usually, there is a family history of intercurrent cardiac illness, including a recent myocardial infarction in an older family member or possibly the death of a family member from cardiac causes that can lead to chest wall pain. In most cases, adequate family therapy should be offered.[126] With the increasing availability of diagnostic methodologies, the diagnosis is far more accurate in these children than it was several decades ago.

Back Pain

Back pain is a common problem in adults and is now becoming a significant health issue in children.[127,128] With high impact sports that involve a greater degree of stress on the back muscles, such as gymnastics, children seem to have a higher degree of back injury.[129] Common back problems include spondylolysis,[130] spondylolisthesis, disk degeneration, disk herniation,[131,132] tumors of the spinal cord, and other diseases, including sickle cell disease. Given that up to 57% of back pain in children is because of a non-organic cause,[133] management in children is usually conservative, with an emphasis on exercises for the back. A study of 177 pediatric patients in the emergency setting found that 77% of the visits were non-pathologic in nature. Imaging was performed in 38% of patients, and positive findings were only noted in 17% of radiographs.[134] Advanced imaging, such as CT or MRI, is warranted in refractory back pain, nighttime pain, association with systemic symptoms, or if sensory or motor radicular symptoms exist. If conservative treatment fails, epidural steroid injections may be considered with appropriate imaging studies. Alternative medicine, including massage therapy and acupuncture, is used for the management of children and adolescents with back pain. These therapies may be especially effective when pain has a myofascial component.

Pelvic Pain

Pelvic pain is often reported in female adolescents.[135] A thorough history has to be obtained, including a history of sexual activity. Children with a history of sexual abuse have a greater

preponderance of chronic pelvic pain.[136] Although not common, a subpopulation of these adolescent girls has a history of endometriosis. This could lead to severe pelvic pain and may need to be treated more aggressively than occasional pelvic pain. Alteration of the ovulatory cycles with birth control pills, as well as the use of strong NSAIDs, should be implemented in these patients. We have had success with the use of active massage therapy and physical therapy as adjuncts for the management of these patients.

Cancer-Related Pain

Cancer remains the second leading cause of death in children. Cancer is diagnosed in more than 12,000 children annually, and 2200 children die each year of this disease.[137] Pain is a common symptom during different phases of cancer treatment. The incidence of cancer-related pain in children at the time of diagnosis is estimated to be 75%, with ongoing pain affecting 50%.[138,139] However, the incidence of pain in the terminal phase of the disease is likely to be higher than 89%.[139] Cancer pain in children is because of several reasons: (1) cancer-related pain (e.g. solid tumor or bony metastatic tumors), (2) pain caused by treatment (e.g. mucositis or surgical pain), and (3) NP secondary to tumor invasion or surgery. Pain caused by treatment and procedural pain are cited as the most frequent types of pain experienced by children with cancer.[140]

Management of pediatric cancer-related pain must be individualized, and caregivers must be empathetic to family needs and concerns. Although more than most pain complaints can be managed by the implementation of the World Health Organization cancer pain ladder paradigm, a significant number of children may require additional therapies or techniques for pain management because of escalating or intractable pain. Only allopathic techniques are discussed in this section. The pediatric doses for most medications are off-label recommendations, and dosing is based on the current pediatric clinical literature.

Oral Medications

Most pain management is achieved with oral maintenance dosing. Around-the-clock scheduling is supplemented with the as-needed analgesic doses for breakthrough pain. Oral techniques include sublingual and transmucosal applications for breakthrough and procedural pain.

Sublingual application of morphine is as effective as intravenous morphine for pediatric postoperative pain.[141] Because sublingual administration avoids hepatic first-pass dosing, it is comparable to intravenous administration. Sublingual morphine may be a suitable alternative to intravenous morphine for pain control in children with cancer-related pain if enteral tolerance or intravenous access is limited. Sublingual buprenorphine, 5–7 μg/kg per dose, has demonstrated similar analgesic efficacy as intravenous morphine, 150 μg/kg.[142] Oxycodone concentrate prepared at 20 mg/mL is appropriate for sublingual application, but small changes in volume can cause large changes in dose. When using this concentrated formulation, an increment of 0.1 mL (from 0.2–0.3 mL) constitutes a 50% increase in dose; an additional 0.1 mL increase (from 0.2–0.4 mL) represents a 100% increase or doubling of the dose administered. Thus prescribing dosing increments that are less than 5 mg may result in variations in the actual amount of oxycodone concentrate delivered. Oxycodone concentrate is not recommended for use in small children.

Intravenous preparations administered via the transmucosal route have been attempted with some success. Oral administration of the intravenous formulation of fentanyl can achieve a pharmacokinetic distribution similar to that of oral transmucosal fentanyl citrate (OTFC) lozenges, but there is much interpatient variability. OTFC lozenges have been used to treat breakthrough and procedural pain in children. Oral mucositis pain treated with 200 μg OTFC lozenges is tolerated but ineffective in adult cancer patients.[143] The effective oral dosage range for postoperative pain management is 10–15 μg/kg for buccal application.[144] Schechter et al.[145] found 15–20 μg/kg of OTFC to be effective for pediatric procedural pain, but one-third of the children experienced vomiting. Transmucosal oxycodone (200 μg/kg) provides relief similar to 10 μg/kg of OTFC for procedure-related pain.[143]

Tablets designed for buccal delivery aim to enhance bioavailability and drug uptake and speed the onset of pain relief. Hepatic first-pass effects are avoided.[146] Studies on fentanyl effervescent buccal tablets have revealed pain relief onset times of 10–15 minutes. The efficacy of the system is dependent on pH because higher plasma levels are achieved at a lower pH. Another benefit of the technique is its discrete nature since the tablets are held between the cheek and gum without telltale evidence of drug intake. The buccal tablet is designed for faster onset than with oral or transmucosal delivery, and thus it is particularly useful in the management of breakthrough pain and may be helpful in cases of anticipated incident pain or potentially noxious activity. This formulation may be an alternative route of administration for those with an inability to swallow medications because of dysphagia or a history of pill aversion.

Integumentary Applications

Transdermal Delivery Systems

Transdermal delivery systems of analgesics and adjuvants can be effective for treating chronic pain. The ideal characteristics of a transdermal delivery system include low molecular weight, lipophilicity, high potency, and reliable patch adhesion.[147] The solubility of the drug in the adhesive, its diffusion coefficient, and its permeability coefficient also play major roles in the time to steady-state release into the skin.[148] The release rates of the agent are dependent on the drug concentration and type of matrix used. A steady-state skin flux is required to yield consistent rates of drug release with zero-order kinetics. Several transdermal systems are available for opioids, α_2-agonists, and anesthetics.

Fentanyl. Transdermal fentanyl was approved for use in children in 2002.[149] A prospective study has cited improvement in pain and quality of life in children 2–16 years of age who had established opioid requirements for cancer and chronic noncancer pain.[150] In pediatric oncology studies, 75%–90% have reported that transdermal fentanyl therapy is "good" or "very good" for the relief of cancer-related pain. These findings suggest that transdermal fentanyl is effective and acceptable for children and their families.[151]

Buprenorphine. Transdermal buprenorphine has been used for the treatment of nociceptive pain and NP. Buprenorphine is a long-acting, partial μ-opioid agonist with antagonistic action at κ-opioid and δ-opioid receptors.[152] Reversal of respiratory depression and sedation from this mixed agonist-antagonist is difficult to achieve with naloxone.[153] Patients with previous opioid use have experienced up to a 30% dose reduction in analgesic requirements. Pediatric tolerance is associated with marked ventilatory reduction with buprenorphine in comparison to morphine and warrants close observation for the initial 24 hours of use.[153]

Clonidine. The transdermal application of clonidine has been the most studied mode of delivery of α_2-agonists. Transdermal

clonidine is well studied in adults, but it is difficult to use for the management of acute or chronic pain. Although neuraxial clonidine has a role in cancer and chronic pain management, it has limited evidence of analgesic efficacy or opioid sparing.[154] However, transdermal application does appear to increase the release of enkephalin-like substances and may therefore be an agent enhancer in balanced analgesia techniques.[155]

Lidocaine Patch

The 5% lidocaine patch is a topical peripheral analgesic that has been approved by the United States FDA for the treatment of postherpetic neuralgia.[156] It has been used for nociceptive pain and NP in non-cancer patients. This technique may be useful for treating malignancy-induced peripheral nerve diseases. Unlike other transdermal delivery systems, which work by systemic uptake, the lidocaine contained in the patch penetrates the skin to act locally on damaged or dysfunctional nerves and soft tissue under the skin. Each 10 × 14 cm 5% lidocaine patch contains 700 mg of lidocaine in an aqueous base. It should be applied to intact skin only because of the risk of systemic uptake. The patch is applied directly or beside the area of pain. Patches can be cut before the release liner is removed to fit the target area. The recommended use is a 12-hour-on, 12-hour-off dosing schedule. It should be used with caution in patients taking oral local anesthetic antiarrhythmic drugs, such as mexiletine, to prevent additive effects. Patients sensitive to amide local anesthetics, such as bupivacaine or ropivacaine, should not use the lidocaine patch. The 5% lidocaine patch has not been studied extensively in children. However, a recent study showed excellent tolerance in patients with vaso-occlusive crisis.[157]

Topical Local Anesthetic

Eutectic Mixture of Local Anesthetics. A four percent tetracaine gel and a eutectic mixture of local anesthetics (EMLA), lidocaine and prilocaine, as a cream or patch have proved effective in relieving pain in children undergoing cancer-related procedures.[158] Studies in children 3–21 years of age have shown these commercial preparations to be beneficial in reducing the pain associated with lumbar puncture, venipuncture, and central port access. These preparations should not be used in premature infants because of the risk of local anesthetic toxicity. The plasma concentrations of lidocaine and prilocaine were well below the toxic level for each agent. Moderate plasma lidocaine levels (4.5–7.5 μg/mL) may cause restlessness, dizziness, blurred vision, or tremors. At high levels (>7.5 μg/mL), lidocaine can produce generalized tonic-clonic seizures.[159] Buccal application of EMLA has not led to local anesthetic toxicity. A study of 12 subjects showed peak concentrations at 40 minutes for lidocaine and prilocaine, and the maximum concentration measured in any subject was 418 ng/mL for lidocaine and 223 ng/mL for prilocaine, each below toxic plasma levels.[160] Methemoglobinemia from prilocaine has been reported with the application of EMLA onto newly regenerated postburn or abraded skin.[161] An occlusive dressing was also used in both cases. Methemoglobin levels below 3% are nontoxic, but skin cyanosis may occur. Levels above 3% can be associated with agitation, and levels higher than 50% result in coma, seizures, arrhythmias, and acidosis.[162] Adverse effects of EMLA include transient skin blanching, erythema, urticaria, allergic contact dermatitis, irritant contact dermatitis, hyperpigmentation, and purpura.

Liposome-Encapsulated Lidocaine. Another option for topical pain control before venipuncture is 4% liposomal lidocaine (L-M-X4), an over-the-counter topical local anesthetic that poses no risk for methemoglobinemia because it does not contain prilocaine. Both 4% tetracaine gel and 4% liposomal lidocaine are effective within 30 minutes of application.

Compounding Topicals

Creams and gels applied topically to the skin target the primary site of pain and discomfort. Pluronic lecithin organogel is a poloxamer used for topical delivery with a bioavailability of 10%–60%.[163] The advantage of using topical medications is that a high concentration of the drug is deposited exactly where it is needed, and purportedly little drug is taken up systemically. This would reduce or eliminate the usual side effects of these medications when administered orally. With a prescription, compounding pharmacies can locally prepare selected agents into topical preparations that are not currently available in the open market. However, variations in concentration, sterility, and lack of FDA regulatory control require caution when used with these agents. Commonly compounded agents for topical application include NSAIDs (e.g. aspirin and ketoprofen), membrane stabilizers (e.g. amitriptyline, clonidine, gabapentin, lidocaine), muscle relaxants (e.g. cyclobenzaprine, baclofen), and antibiotics (e.g. amoxicillin and clavulanate). The topical application of clonidine has been shown to be beneficial in children with cancer. The successful use of topical clonidine ointment in a child with herpetic neuralgia after bone marrow transplantation relieved the associated pain, pruritus, and insomnia.[164]

Parenteral Medications

Subcutaneous Infusions

Subcutaneous infusions are considered equivalent to intravenous infusions once a steady plasma state is achieved. Up to 5 mL/h can be absorbed by subcutaneous infusion, thus making this route of delivery feasible for pediatric cancer pain management.[165] This technique should be considered when oral management is not practical, but long-term opioid requirements have been substantiated. The success of this technique depends on patient selection, ongoing home health care support, and the choice of analgesic drug. Highly concentrated solutions were well tolerated and resulted in lower infusion rates. Opioid concentrations of up to 30 mg/mL have been used in adults and tolerated for up to seven days, with rotation of the site of delivery every 72 hours.[166] Patient-controlled analgesia (PCA) can be delivered by subcutaneous infusion if intravenous access is not possible. Access via small-caliber needles, such as a 27-gauge butterfly needle, or access with a 22-gauge tunneled intravenous catheter can be maintained in situ for infusion. Combined subcutaneous and intravenous infusion techniques may be indicated when venous access is limited, but titration of individual agents is needed.

Intravenous Infusions

Outpatient use of intravenous opioids and adjuvants is indicated for gastroenteric intolerance, escalating pain inadequately controlled with adjusted oral medications or intolerable side effects from oral agents. Intravenous access via peripheral catheters or central ports and catheters is often used in situ for chemotherapy or nutrition. Because of limited access, the coadministration of analgesics with parenteral nutrition should be considered to limit the interruption of access and control the risk of infection. Trissel and coworkers[167] studied the compatibility of parenteral nutrition solutions with selected drugs during simulated Y-site administration. They reported that parenteral nutrition solutions are compatible with many agents, including opioids, for 4 hours

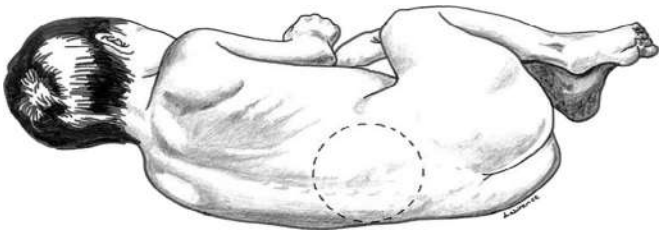
at 23°C, and morphine, fentanyl, hydromorphone, and oxymorphone are compatible via a filter with total parenteral nutrition. Despite visual compatibility testing, admixtures of analgesics in nutritive solutions are not advised. Delivery of the analgesic drug at the Y-site in the central catheter system was the best.

Neuraxial Delivery System

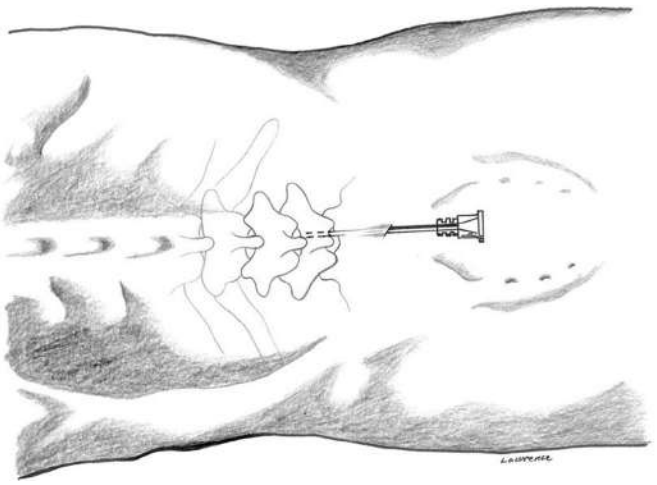
Children with solid tumor disease compounded by extension of the neoplasm to peripheral nerves or nerve roots at the neuraxis are more likely to require larger opioid doses than children with nonsolid tumors (e.g. leukemia).[168] It has been proposed that hyperalgesia and NP are associated with reduced opioid antinociception and contribute to the massive dose requirements. Systemic morphine doses as high as 518 mg/kg/h have been cited in the pediatric literature.[169] The use of neuraxial (epidural and intrathecal) analgesia is indicated for the management of cancer pain when other routes are impractical or yield intolerable side effects. Retrospective reviews of adult and pediatric populations suggest that neuraxial (epidural or intrathecal) infections are rare. A review by Strafford et al.[170] revealed no serious complications in 1620 general pediatric subjects who underwent short-term epidural catheterization. Bacterial colonization of caudal and lumbar epidural catheters in children has been studied prospectively. Kost-Byerly et al. associates[171] found a 35% colonization rate of epidural catheters and an 11% occurrence of local inflammatory changes when catheters remained in situ for up to five days (mean duration, three days).

Long-standing epidural analgesia is effective and safe for the spectrum of cancer-related pain, as well as for terminally ill patients, but proper management of infection risk and strict catheter care are imperative. Tunneling of epidural catheters is performed to decrease the likelihood of infection, improve catheter stability, and aid patient mobility during prolonged administration of neuraxial analgesia. A percutaneously inserted tunneled catheter connected to an externalized pump is a feasible technique for prolonged care (Figs 43.5 to 43.8). Use of a 0.2 μm filter, regular changing of the pump tubing, and weekly or biweekly dressing site care performed with sterile technique may decrease the risk of infection. In a retrospective pediatric study of 25 children, the externalized catheters remained in place for up to 240 days without the occurrence of an epidural abscess or meningitis.[172] The duration of tunneled catheter use by region was 22 days for thoracic (three catheters), 240 days for lumbar (12 catheters), and 42 days for caudal (10 catheters).

The risks and benefits of tunneled epidural analgesia in patients with cancer and coexisting NPs should be closely weighed. It is recommended that totally implanted systems be considered for patients with NP.[173] The signs and symptoms of epidural infection include fever, escalating back pain, back or neck ache, MRI evidence of inflammation, elevated sedimentation rate, C-reactive protein level, and white blood cell count. Superficial infection may include local tenderness, erythema, subcutaneous phlegmon,



• **Figure 43.5** Positioning for epidural placement in a child.

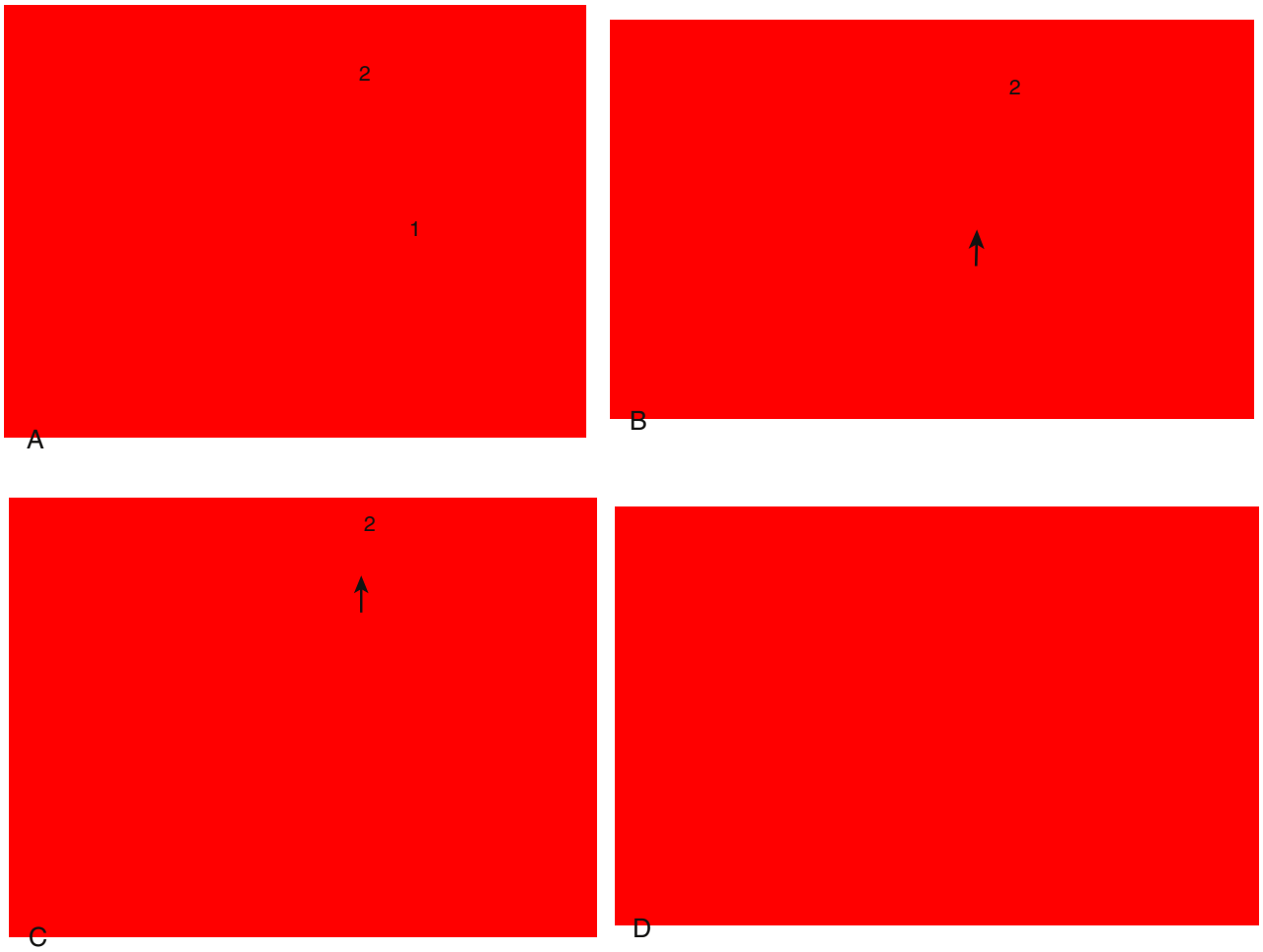


• **Figure 43.6** Percutaneous placement of an epidural.

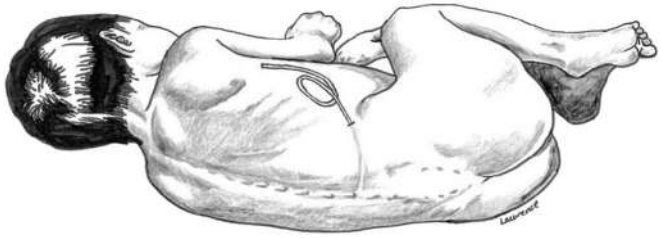
and exudates at the exit site. The presence of an epidural abscess is confirmed by aspiration of exudates, an epidurogram with dye loculation at the catheter tip or retrograde flow, positive culture of the catheter tip, or positive culture of epidural lavage material. Removal of the epidural catheter is indicated in those with temperatures of 39°C or higher, and if any of the aforementioned signs and symptoms are present. Superficial infections are treated with a 7–14 day course of antibiotics. Epidural abscess management includes six weeks or more of intravenous antibiotics with or without neurosurgical drainage of the epidural abscess.[174]

Analgesia via the neuraxial route is associated with less sedation and fewer adverse effects because significantly smaller doses of opioids are used. Spinal opioids provide selective pain blockade without sympathetic nervous system blockade.[175] The more hydrophilic or hydrophobic opioids have limited uptake in epidural fat and its vasculature and yield greater rostral spread in cerebrospinal fluid (CSF) than hydrophobic lipophilic opioids such as fentanyl. Intrathecal opioids bypass the bloodstream and have a direct CSF spread. The onset of action of intrathecal morphine is 15–45 minutes. Delayed respiratory depression is a concern for spinal opioids. Gregory and coworkers[176] noted that peak morphine levels in the medulla coincided with peak ventilatory depression 6 hours after lumbar intrathecal injection. Nichols et al.[177] injected 0.020 mg/kg of morphine into the intrathecal space at the L4-5 interspace; this showed the greatest depressed ventilatory response to carbon dioxide at 6 hours that persisted for up to 18 hours, and infants 4–12 months of age responded in a similar fashion to children 2–15 years old. Other side effects do not appear to be dose dependent and include nausea, vomiting, pruritus, and urinary retention. However, side effects are worse with intrathecal administration than with epidural opioids.

The most commonly used adjuvants to improve pain and decrease opioid requirements include local anesthetics and α_2-agonists. The literature has consistently documented appreciable pain control when clonidine is administered by the intravenous and neuraxial routes as an adjuvant to opioids or local anesthetics.[178] The benefits of clonidine as an adjuvant include the following: (1) reduction in the amount of opioid required for analgesia and thus a probable decrease in side effects because of opioids; (2) titrated sedation and anxiolysis without additive respiratory depression when administered in combination with opioids; and (3) vasodilation and improved circulation of the cerebral, coronary, and visceral vascular beds.[178]



• **Figure 43.7** **A,** The epidural catheter is threaded, and the second needle is tunneled to exit the initial (first needle) entry site. This is performed before the removal of the first needle to avoid shearing of the catheter. **B,** The second needle acts as a trocar. This step can be repeated for a longer tunneled section that can be brought to the anterior. **C,** The first needle is removed, and the catheter is threaded in a retrograde fashion into the tip of the second needle and exits the hub. **D,** The second needle is then withdrawn.



• **Figure 43.8** The externalized catheter can be connected to a balloon-type pump or patient-controlled analgesia apparatus.

Continuous intravenous infusion of clonidine has been cited as a safe adjuvant for pain control in adult and pediatric populations, but the question of long-term impact on neurobehavioral function has been raised. The amount of opioid required by patients experiencing procedural pain was reduced by 30%. Hemodynamic stability was maintained within normal limits because patients experienced less than a 10% change in mean blood pressure. Clonidine has the further advantage of producing sedation associated with only small reductions in minute ventilation and has no effect on hypercapnic or hypoxic respiratory drive.[179]

Pain in Terminal Illness

There has recently been a surge in treatment modalities for pain, and treatment of children is now part of a cure-oriented and technology-based healthcare system. Recently, with the involvement of facilities such as hospices, the care of terminally ill children has been based on the same philosophy as that for adults.[180] Pain can be a significant problem in children who require terminal care. When some children with a life-threatening illness have a significant setback, there may be no firm criteria to stop treatment and direct palliative care.

Alternative novel methods for providing analgesia have been used by our pain service for children who do not have intravenous access. Nebulized opioids[181] or transdermal delivery systems have been used to offset pain in children with intractable pain. Adverse effects associated with the long-term use of opioids include tolerance and withdrawal. Careful rotation of opioids, along with the judicious use of other adjuvants such as *N*-methyl-D-aspartate receptor antagonists, should be considered in the care of children and adolescents.

Several approaches to pain management can be taken depending on the state of the patient, involvement of the disease process, and the general state of the caregivers. PCA has been widely used in our institution for homebound patients with terminal cancers. Smaller, more user-friendly pumps have been devised for easy programming

and less frequent changes. In patients without venous access, we recommend the use of subcutaneous PCA. Other drugs are useful for terminally ill children. NSAIDs and steroids are particularly helpful in the management of bone pain because of metastasis. Carbamazepine, gabapentin, pregabalin, and TCAs are useful in the management of NP. Hypnosis, biofeedback, and distraction techniques can be used effectively in children who are not heavily sedated.

A child's view of death is very different from that of an adult. There is a consistent progression of the conceptual aspects of death as children grow older. Finally, a school-age child understands the permanence of death. Home care may be useful for families to cope with grief and sorrow. It also allows other siblings to spend some time with the loved one. A home care coordinator should be available to manage adverse conditions. Knowing the family helps the coordinator understand the goals of the family. One basic tenet of hospice care is to enable the patient to lead a full life, of the best quality, for whatever time remains. Cooperation between the family and caregiver should allow the child to die with as much dignity as possible. It is the responsibility of the home coordinator to provide caregivers with sufficient information about the management of pain.

Targeted and titrated delivery of antinociception is becoming a reality, as more receptor-specific agents have been devised. More pediatric studies are needed to substantiate the use of the agents and techniques discussed for the management of cancer-related pain in children and adolescents. Regardless of how creative advancements in pain management may become, patient safety must be put first. Novel applications of older agents have broadened the armamentarium of pediatric anesthesiologists and pain management specialists.

Conclusion

Chronic pain in children is underrecognized. Early diagnosis and intervention help ensure adequate recovery. A dedicated CBT program is a helpful adjunct to medical management and physical therapy. Complementary therapy, including massage, acupuncture, and biofeedback, can be used to reduce pain and decrease the need for additional pain medication. Interventional techniques, including serial nerve blocks, can be helpful in refractory cases. A dedicated pain treatment center facilitates adequate and early management of pain in children to ensure rapid recovery to normal function. Future research in the paradigms for managing chronic pain in children needs to be conducted to shape treatment strategies and develop novel approaches to care for this challenging group of patients.

Key Points

- Assessment of pain in children involves a multi-disciplinary approach specifically tailored to the biomedical, psychological, and social elements of each patient and family.
- Psychological interventions can treat pain effectively by modifying the child's cognitive, affective, and sensory experiences of pain, behavior in response to pain, and environmental and interactional factors that influence the pain experience.
- Pediatric CRPS management includes physical therapy, pharmacologic therapy, regional and sympathetic blockade, neuromodulation, and psychological interventions.
- Headaches in children should be evaluated carefully to determine their cause before initiating treatment.
- Headache management includes pharmacologic therapy, CBT, peripheral nerve blocks, and complementary therapy.
- FAP is best treated with CBT, anti-depressants, and serial rectus sheath or transversus abdominis plane blocks.
- Noncardiac chest wall pain may be treated with nonsteroidal anti-inflammatory drugs, CBT, and complementary techniques, including acupuncture and massage therapy. Nerve blocks may be used in refractory cases.
- Common causes of pediatric back pain include spondylolysis, spondylolisthesis, disk degeneration, disk herniation, tumors of the spinal cord, and other diseases, including sickle cell disease.
- Management of pediatric cancer-related pain is individualized and based on family needs and concerns.
- Pain can pose a significant problem in children who require terminal care. Approaches to pain management are based on the state of the patient, involvement of the disease process, and the general state of the caregivers.

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Geriatric Pain Management

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Introduction

The global population is aging rapidly, with demographic shifts resulting in the proportion of adults ages over 65 years and above significantly increasing globally from 6.1% to 8.8%.[1] The rising prevalence of chronic conditions, of which persistent pain is a common and distressing symptom,[2] is strongly associated with advancing age. Multimorbidity, the presence of three or more interacting chronic conditions, is a major contributor to persistent pain.[3] Persistent pain, which exists beyond the expected healing time, often has no identifiable physical cause, and bothersome pain afflicts 52.9% or 18.7 million older adults.[4] In nursing home residents, Lapane and colleagues found that 27.9% reported mild pain, 46.6% moderate pain, and 25.6% reported severe pain.[5] Besides increasing age, risk factors associated with the development of persistent pain include sex, as women are more likely to report greater persistent pain than men,[6] low income,[7] mental health conditions such as depression and anxiety, and obesity.[8] Prevalent causes of persistent pain in older adults are osteoarthritis, cancer, injuries/falls, chronic low back pain, and diabetes (i.e. diabetic neuropathy).[9]

Conditions such as frailty[10] and the residual effects of emerging health threats like that of communicable diseases such as Ebola and coronavirus-2 (SARS-CoV-2; known as COVID-19) may increase the risk and burden of chronic pain, especially in older adults who make up 80% to 95% of all COVID-19 fatalities in the United States and Europe, respectively.[11] In fact, some speculate that COVID-19 will indeed increase chronic pain overall in the general population citing infections, inflammation, and psychological triggers as underlying drivers.[12] This will likely result in new challenges in effectively managing multiple types of pain in older adults and perhaps necessitate multidisciplinary rehabilitation[13] and implementation of COVID-19 pain guidelines.[14]

Unrelieved persistent pain in later life has many debilitating consequences, including psychological distress, social isolation, impaired sleep quality, physical disability, increased fall risk, and loss of independence.[3,15] Optimizing pain management is important, but obstacles to the identification, assessment, and management of pain underscore the importance of providing close attention to older patients.[16] Consideration of an older adult's health, functional capacities, and cognition are essential in relation to the patient's ability to reliably report pain, and when formulating a pain management plan where they can engage in their care. This chapter provides the reader with an overview of the most current perspectives on the assessment and management of persistent pain in older adults and describes challenges healthcare providers may encounter when delivering pain care to older persons.

Barriers to Successful Pain Management in the Older Patient

Physiologic and Sensory Impairments

Anatomic and physiologic changes normally observed as part of the aging process are progressive, and concomitant injury or disease can rapidly worsen the health status of the older individual. Changes in pain transmission, tolerance, and threshold can decrease the speed of processing nociceptive stimuli and thus reduce older adults' ability to sense and respond to early pain stimuli.[17] Therefore older adults may have a greater susceptibility to burns and other injuries such as lacerations because they are not as likely to sense the initial pain and do not respond (e.g. removing hand) as quickly as younger adults. These alterations may reflect aging-associated reductions in peripheral intraepidermal nerve fiber density and small fiber neuropathy and contribute to sensory losses and pain. Additionally, sensory impairments are common among older adults and can negatively impact the management of pain.[18] Visual impairments such as cataracts, macular degeneration, and diabetic retinopathy that can make it difficult to read prescription labels or participate in recommended exercise programs.[18] Use of good lighting in patient exam rooms, asking older patients to wear eyeglasses, and providing reading materials in large font can help mitigate the negative impact of poor vision on pain care. Hearing impairments are also common.[19] Handheld amplifiers, speaking slowly while facing the older patient directly to allow for lip reading, and providing written instructions can help to decrease the negative impact of hearing loss when managing pain among older adults with hearing deficits.

Cognitive Impairment

Cognitive deficits are common in later life but remain under recognized and under treated.[20] Although a recent study suggests pain treatment in those with moderate-severe dementia has improved, 45% of residents experienced moderate to severe pain[21] and still less likely to receive pain treatment than cognitively intact

residents.[22–24] Numerous barriers exist to provide appropriate analgesia to this group, both at the patient and provider levels. Communication is a major challenge to both assessing and managing pain in this patient population, and cognitively impaired older patients tend to under report pain.[25] Manifestation of pain in cognitively impaired older patients can also vary, from behavioral disturbances, such as lethargy and physical aggression, to more expected reactions such as groaning and grimacing.[26] Cognitive impairment creates additional challenges to assessing pain in older adults. As the severity of cognitive impairment increases, a patient's ability to self-report pain diminishes, particularly if experiencing multiple cognitive issues such as delirium, agitation, and dementia.[23,27]

Caregiving

As the prevalence of pain increases among older adults, so does the demand for caregivers, especially informal caregivers. Informal caregivers and unpaid caregivers, such as family members, relatives, friends, and partners, who take care of loved ones are playing a greater role in their managing the older adult's condition and symptoms.[28] One of the most challenging tasks for caregivers is the management of pain, and caregivers encounter a variety of barriers related to the management of their loved one's pain, including lack of education, ineffective communication with providers, and their own wellbeing. Attention to these needs is essential as the caregiver could be a great asset or adjunct to pain management across the life span.[29] Adequate pain management skills training and education of caregivers can improve patient outcomes.[30]

Beliefs and Attitudes About Aging and Pain

Certain beliefs that older adults and providers have about pain and pain treatments may negatively influence their expectations, behaviors, and decisions regarding treatment recommendations and engagement and/or adherence. As noted, many older individuals consider pain as a natural part of getting older, and rather than seek care,[31] often consider it as something to bear.[32] Beliefs such as these can lead to stoicism or acceptance of the status quo.[32] Although relatively little research has examined whether these beliefs are associated with specific health behaviors, beliefs can negatively affect an older patient's willingness to seek treatment or adhere with a recommended treatment plan.[31] Prior research has also shown that some older adults endorse beliefs and fears (e.g. addiction and dependence) about pain medications that decrease their willingness to engage in or adhere with pharmacologic interventions.[33–34] These concerns may also be voiced by older patients' caregivers, often a spouse or an adult child. Thus some healthcare providers may be more reluctant to prescribe opioid medications for older patients with non-cancer pain because of a fear of causing patient harm.[35] Older adults with pain who endorse this belief report minimizing medication use except when the pain is "very bad."[34] Others show that severe pain is associated with opioid and psychotropic medication use in older adults.[36] Providers should be diligent in ascertaining these beliefs during regular clinical encounters and provide research-based education to counter ageist misconceptions. Within a pain management context, this would mean asking patients open questions about their views on the origins and cause of pain, the meaning and impact of pain, their views about treatment and treatment goals, and educational needs.

Cultural Differences

Pain assessment and management must be individualized and consider an older person's culture and language. Pain specialists may provide pain care to patients of different racial groups, cultures, religions, and recent migrants. Pain beliefs and behaviors are further influences by factors such as acculturation, time since migration, and sex. Understanding and appreciating cultural diversity in older patients' pain beliefs and behaviors can help in the provision of appropriate and acceptable pain care.[37] However, this can be challenging when little evidence is available to support bias-free best practices in diverse groups.

Older adults who are members of minority groups (race, religion, gender) face particular barriers to adequate pain management. Some evidence suggests that older adults of some ethnic minority groups (1) are more reluctant to report pain, (2) have a higher prevalence of more severe, persistent pain, functional limitations, and health consequences, (3) may be less likely to seek help for their pain, and (4) are less likely to receive consistent and adequate medical treatment.[38–39] Reasons for the established disparities in pain management are complex but include socioeconomic disadvantage, discriminatory healthcare systems, and healthcare policies, and misguided pain beliefs and behaviors. We acknowledge that "minority" is not synonymous with socioeconomic disadvantage but is an important consideration for many older adults. Socioeconomic disadvantage and broader discriminatory systems cannot easily be changed by providers but can be improved by providers taking the time to understand each patient's circumstance and perspective. A simple cultural framework that applicable in clinical settings is the "ASKED MYSELF" mnemonic, which has been adapted for Black Americans with pain but can be easily used in multiple racial/ethnic groups.[40] Each letter of the mnemonic guides providers through knowledge- and attitude-based questions about their ability to care for Black Americans with pain; for example, A = Awareness: Am I **aware** that Black Americans experience immense pain disparities related to diagnosis, treatment, and outcomes?[(p. 66)], K = Knowledge: Am I **knowledgeable** about pain-related beliefs, practices, and cultural values, such as the use of spirituality?[(p. 67)]

Language barriers may require additional help in communicating or the services of interpreters ("translators") within health care. This also includes having validated pain assessment scales translated into multiple languages. Recent and older migrants may find health care challenging if they are not fluent in the country's dominant language and may rely on family or friends as means of accessing health care and communication with providers. An informal interpreter may influence a consultation, not only because of the accuracy of language translation but also because of cultural beliefs and social roles in the healthcare interaction, which may be influenced by age, sex, and social position.[41] Not only must providers be aware of language barriers but also the different ways in which cultural groups verbally and non-verbally communicate pain and its impact.

Access to Healthcare Services and Technology

The proportion of older adults in the population is increasing more rapidly in rural areas where access to health services is limited and expensive. This has motivated efforts to identify new and efficient healthcare delivery models, especially for chronic condition management, such as pain management.[42] There is a potential for technology to overcome these barriers by decreasing or

eliminating the need for patients or providers to travel to deliver or attend to health services and pain management.[43] In addition, technology can help facilitate and promote self-management of pain, which is routinely encouraged for chronic pain.[43–44] Technology, such as digital devices (e.g. smartphones, tablets, computers, voice-assistants, or other internet-enabled devices) and software (e.g. email, video-chat applications, online healthcare portals, social networking/media) can be used to improve patient care through more effective monitoring of treatment outcomes, enhanced patient-provider communication, and by providing new ways to deliver treatment.[9,43] These technologies are referred to as eHealth (electronic health) or mHealth (mobile health). eHealth is a broad concept that often encompasses telehealth and telecare technologies but can also include online education and patient-health professional consultations. Telecare involves monitoring aspects of patient's activity (e.g. fall alarms, motion sensors, wearable activity trackers), while telehealth technologies require active involvement from the patient to take readings (e.g. blood pressure and online pain diary) that are regularly submitted to providers for review.[42] Other technologies, such as virtual reality, can supplement as adjuvant non-pharmacologic treatment options in older adults.[45] Implementation of eHealth or other technologies to support pain management should be gradual and begin with supplementation of existing care and should be mindful of a patient's circumstances, capability, current use of everyday technology, and preferences. The acceptance of technology among older adults may relate to existing personal and social contact levels and may be greater where technologic help is not perceived as replacing in person care.[44]

Assessing Pain in the Older Adult

Although accurate assessment of pain is the critical first step in the pain management process, this step can challenge even seasoned clinicians. Older adults typically present with multiple symptoms and medical conditions, leaving healthcare providers little time to address pain in the context of a busy office visit. We described the implications of these barriers in the prior sections of this chapter. Recognizing these challenges and taking steps to address them is an important first step in the assessment and management of pain in older adults.

The key to developing an effective treatment plan is a comprehensive evaluation for the underlying cause of pain, pain characteristics, and impact on physical and psychosocial function and quality of life. Pain and common associated factors (e.g. anxiety, depression, beliefs, insomnia, biomechanical issues) can cause impairment or dysfunction, and each should be considered. Identifying underlying diseases known to be painful (Table 44.1) and current and prior prescription and over-the-counter analgesic history (regarding effectiveness and adverse effects) provides

TABLE 44.1 Types of Pain and Management Approaches

Type of Pain & Description	Pain Characteristics & Related Presentation	Example Pain Conditions
Nociceptive - Responds best to non-opioid (e.g. acetaminophen, NSAIDs) and opioid medications along with non-pharmacologic therapies (e.g. heat, acupuncture, massage, exercise, aquatic therapy, TENS).		
Somatic: tissue injury of bones, soft tissue, joints, muscles	Well-localized, constant; aching, stabbing, gnawing, throbbing	Arthritis, low back pain, tendonitis, acute postoperative, fracture, bone metastases
Visceral: tissue injury of visceral organs including heart, lungs, testes, and biliary system	Diffuse, poorly localized, referred to other sites, intermittent, paroxysmal; dull, colicky, squeezing, deep, cramping; often accompanied by nausea, vomiting, diaphoresis	Renal colic, constipation, urinary tract infection
Neuropathic - Often treated with adjuvant medications, e.g. anti-convulsants, (tricyclic anti-depressants, selective serotonin, and norepinephrine reuptake inhibitors) and opioids if needed; non-pharmacologic therapy that act on nervous system mechanisms is important (e.g. neurostimulation, CBT).		
Peripheral nervous system: injury to the nervous system—nerves	Prolonged, usually constant, but can have paroxysms; sharp, burning, pricking, tingling, pins-and-needles, shooting electric-shock-like; associated with other sensory disturbances, such as paresthesia and dysesthesias; allodynia, hyperalgesia, impaired motor function, atrophy, or abnormal deep tendon reflexes	Cervical or lumbar radiculopathy, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, phantom limb pain, herniated intervertebral disc, drug toxicities
Central nervous system: injury to the nervous system at the brain or spinal cord level	Same as above. Pain may be experienced above, below, or at the level of the spinal cord	Central post-stroke syndrome; spinal cord injury-related neuropathic pain; multiple sclerosis
Mixed or Nociplastic - Treatment may consist of non-pharmacologic therapy (e.g. exercise, CBT), non-opioids, opioids, and adjuvant medications to manage multiple characteristics of pain		
Central, undetermined, or mixed: pain from altered nociception despite no clear evidence of actual or threatened tissue damage; neurologic dysfunction and/or nociceptive issues and uncertain causes	No identifiable pathologic processes or symptoms out of proportion to identifiable organic pathology; widespread musculoskeletal pain, stiffness, and weakness; fatigue, sleep disturbance; taut bands of muscles and trigger points; sensitivity to sensory stimuli	Myofascial pain syndrome, somatoform pain disorders, fibromyalgia; post-stroke pain; temporomandibular joint dysfunction, tension headache

CBT, Cognitive behavior therapy; *NSAIDs*, nonsteroidal anti-inflammatory; *TENS*, transcutaneous electrical nerve stimulation.
Adapted from Reuben et al. *Geriatrics at Your Fingertips*. 22nd edition. New York: American Geriatrics Society; 2020. Used with permission from the American Geriatrics Society.

important information to guide treatment planning. Assessment of basic and instrumental activities of daily living helps determine the impact of the pain on function. A complete physical examination of the pain source and the musculoskeletal, peripheral vascular, and neurologic systems is important to identify treatment targets. The physical examination should also target potential pain contributors (e.g. leg length discrepancy, myofascial pain, sacroiliac joint syndrome) that can be addressed. Although laboratory and diagnostic tests can be used to establish an etiologic diagnosis, radiographic evidence of degenerative joint disease is often not associated with pain severity, and imaging studies may not be justified.[46] This aligns with the International Association for the Study of Pain's updated definition of pain, "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[47]

Older patients should be asked routinely about pain (and because many older adults will not endorse experiencing "pain," they should also be queried about the presence of ache, hurting, discomfort, or burning sensations) at each visit. Description of pain is essential to determine the type of pain for treatment planning. Gathering information on physical and psychosocial function is important to fully understand pain and its impact and guide treatment planning.[15] Table 44.2 and the following section outline age-appropriate approaches and assessment tools for use with both cognitively intact and cognitively impaired older adults.

Assessment Tools

A wide range of assessment tools is available for use with older adults, many of which are well validated. Unidimensional pain scales (e.g. those that assess pain intensity only) are feasible for use in the context of a busy clinical encounter. Examples include the verbal pain descriptor (none, mild, moderate, or severe) and numeric rating (0–5 or 0–10) scales, the Pain Thermometer, and Faces Pain Scale, all of which have been validated for use in older populations to include individuals with mild to moderate cognitive impairment.[48] Using instruments that capture the multidimensional experience of pain to include its impact on function is strongly recommended.[49] Brief measures that assess pain and its impact on function that can be readily incorporated into geriatric pain practice include the Brief Pain Inventory-Short Form (BPI-SF), the Pain, Enjoyment, and General Activity (PEG) Scale, or the Functional Pain Scale (FPS).[50]

Assessing Pain in Older Patients With Cognitive Impairment

Cognitive impairment occurring in dementia can alter the pain experience and contribute to difficulty interpreting pain signals increasing vulnerability to pain.[51] Pain assessment in older patients with cognitive impairment requires an adapted approach to recognize potential pain problems that include a search for diagnoses or conditions known to be painful, observe pain-related behaviors and changes in interactions, activity patterns or routines, or mental status, obtain proxy input from family or caregivers, and ultimately, if necessary, use an analgesic trial to validate pain presence.[16,52] These steps are amplified in Table 44.2.

Behaviors that suggest underlying pain include facial expressions (grimacing, frowning), vocalizations (noisy breathing), changes in activity patterns (eating, sleeping), changes in mental status (confusion, irritability), body movements (guarding, bracing), and interpersonal interactions (aggressive, disruptive, social withdrawal).[51] Numerous observational tools are available and can help providers assess pain among older patients who cannot communicate verbally. The most recent systematic review of behavioral pain scales identified the strongest supported tools as the Pain Assessment IN Advanced Dementia (PAINAD), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), and DOLOPLUS-2.[51] Two new tools that attempt to delineate the behaviors that are best to identify pain in those with dementia may guide practice recommendations in the future.[53–54] Observation of behaviors should occur during movement and not just at rest.[16] The information collected using pain assessment or behavior scales will help in developing a comprehensive management plan.

Management of Pain in Older Adults

Various biologic, social, and psychological factors contribute to pain, and whether acute or chronic, require a strategic multimodal pain management plan that integrates best evidence with patient preferences. Treatment should be viewed broadly, not focused only on reducing pain intensity but also in addressing contributing factors and preventing long-term effects of pain. Developing a pain management plan involves evaluation of the patient goals for outcomes and treatment options with risk/benefit analysis to ensure safety and quality. A multimodal management plan is a personalized approach that includes multiple non-pharmacological strategies, medications, techniques, and pain management devices to gain the best control of pain (Fig. 44.1). This treatment plan might always include analgesics but should start with non-pharmacologic interventions, as many are accessible, inexpensive, easy to use, and result in fewer side effects.[55] Recent guidelines from the American College of Rheumatology recommend managing osteoarthritis pain using a comprehensive approach.[56]

Non-Pharmacologic Management and Self-Management

With rising concerns of opioid misuse and the greater likelihood of older adults to experience adverse effects from polypharmacy and medication interactions, consider non-pharmacologic pain management as early options when managing pain in the older patient. A range of physical and psychological modalities are available for persistent pain and include physical techniques such as repositioning, use of heat and cold, massage, transcutaneous electrical stimulation and therapeutic touch, and psychological therapies, such as distraction, relaxation, and guided imagery.[57–58] Research evaluating their use in the cognitively impaired population is limited; however, based on their efficacy in cognitively intact older adults, their general use can be inferred in this population. Individualize the appropriate complementary therapy as the level of cognitive impairment may limit the use of certain interventions, particularly behavioral modifications.

Physical activity and exercise can help reduce pain-related disability and increase physical function and quality of life for older adults with persistent pain. With regular moderate exercise (at least 150 minutes per week for all United States adults), older adults can increase physical function, slow the progression of physical deterioration, and improve range of motion. However, fear of pain and pain itself is often cited as a barrier to initiating and maintaining physical activity and exercise, and this can result in

TABLE 44.2 Steps for Focused Pain Assessments in Older Adults

Cognitively Intact and/or Able to Self-Report	Cognitively Impaired and Unable to Self-Report
Step 0: Determine willingness, ability, and reliability to provide self-report pain by observing coherence of verbal communication, assessing conceptual understanding on how to use a pain scale by asking where mild pain and severe pain are represented on a zero to ten pain scale, and/or administering a cognitive screen, such as the Mini-COG or mini-mental status exam (MMSE). Older adults who score 18 or above on MMSE can usually reliably self-report pain.	**Step 0: Determine willingness, ability, and reliability to provide self-report pain, and also note if there is a diagnosis of cognitive impairment or dementia**. Some older adults with mild-moderate dementia remain able to self-report; in these situations, refer to the left column. If unable to self-report, continue with steps one to five in this column.
Step 1: Be attentive or identify potential sources and causes of pain by reviewing the health history, physical examination, diagnostic tests, laboratory values, and medication history. There may be multiple sources/locations and types of pain resulting from multiple morbidities. See Table 44.2.	**Step 1: Search for possible etiologies of pain** such as a history of pain conditions, pathological (e.g., chronic diseases, infections), procedural (e.g., postoperative pain, blood pressure cuff pain, wound care), accidental (e.g., skin tears), trauma (e.g., falls, concussions, elder abuse), and emotional causes (e.g., depression, anxiety, PTSD).
Step 2: Determine presence/absence and intensity of pain by asking older adult if s/he is experiencing pain "right now" or "at this moment." Alternative descriptors, such as ache, sore, hurt, and discomfort, should be used if "pain" is denied. **Measure self-reported pain intensity using a valid, reliable, and preferred pain scale** such as the Faces Pain Rating Scalerevised (FPS-r), Revised Iowa Pain Thermometer (IPT-R), Verbal Descriptor Scale, or Numeric Rating Scale.[48,73] The verbal descriptor scale with or without a thermometer is preferred by most older adults, although best practice is to ask the older adult the tool they prefer to use. Also, ask about location and radiation, duration, frequency or pattern, and precipitating and ameliorating factors to help determine the cause.	**Step 2: Attempt self-report to determine the presence and intensity of pain.** A patient with limited verbal and cognitive skills may provide a simple yes/no, other vocalizations, or gestures to communicate pain. *See adjacent text.*
Step 3: Assess the impact of pain on function to determine pain tolerability and interference with life activities. Different patients will find different pain intensities more tolerable, and this information is essential to establish pain treatment goals. Use established measures such as the BPI-SF, the FPS, or the PEG.[50]	**Step 3: Observe for potential pain behaviors using an appropriate pain behavior observation tool.** Observation of facial expressions, verbalizations/vocalizations, body movements, changes in interpersonal interactions, changes in activity patterns or routines, and mental status changes may help confirm pain. When there is a change in older adults' behavior, consider pain as an etiology. Select a recommended pain behavior observation tools, such as the Pain Assessment in Advanced Dementia Scale (PAINAD) or the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC-II) to consistently evaluate pain-related behaviors;[16] other pain behavior tools may be appropriate and clinically usable for different populations, settings of care, and languages.
Step 4: When appropriate, engage the patient care team and family or unpaid caregivers in the assessment. The patient care team can include the patient, selected family and significant others, caregivers, and healthcare providers who may be able to provide additional recognition of the presence of pain and its impact on function when the older adult is reluctant to report pain.	**Step 4: Engage the patient care team and family to obtain proxy reporting** (e.g., nurse, certified nursing assistant) about older adult's usual behavior, communication style, functional patterns, and mood. Proxies need recent knowledge of pain problems, activity level, and normative behavior to recognize subtle changes that may otherwise go unnoticed.[99]
Step 5: Develop and implement a comprehensive plan for management guided by realistic goals for comfort, function, and mood. A comprehensive plan is driven by patients' goals and preferences for care and integrates both pharmacological and non-pharmacological interventions. Continue to re-assess regularly based on pain severity and type using the same self-report pain intensity scale.	**Step 5: Initiate analgesic trial** if (a) pain is the suspected cause of behaviors as demonstrated by a pain behavior observation tool, (b) behaviors do not respond to non-drug interventions, or (c) etiology known to be painful and other causes ruled out. The type of pain suspected (e.g., nociceptive or neuropathic), comorbidities, and contraindications determine the stepped approach taken. The trial length can range from one to seven days. Improved behavior after administration of an analgesic is support for assuming pain is present; then develop a multimodal treatment plan guided by attainable goals for continued comfort, function, mood, and behavioral improvement. Continue to re-assess behaviors using the same pain behavior observation tool. If unresponsive to analgesic trial, explore other potential causes and/or consult a pain management specialist.

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the avoidance of movement and consequentially reduced physical function and greater pain.[59] Prescribed exercise should be individualized, supervised for those with either severe pain or significant physical disability, and include flexibility, strength, and endurance exercises.[55] Alternative movement-based therapies, such as tai chi and yoga are safe and low impact strategies to engage older adults in physical activity.[55]

Poor coping skills and negative beliefs about pain and its management make managing persistent pain difficult regardless of patient age. Psychological therapies, such as cognitive behavior therapy (CBT), acceptance and commitment therapy, and mindfulness promote positive pain coping, beliefs, and behaviors. Consideration of the treatment goals of older patients is important for these therapies, such as increased social interaction and functional independence for activities of daily living. CBT aims to promote and reinforce self-management and positive health behaviors and pain beliefs.[55] CBT is recommended for older adults with persistent pain disorders and can be provided as a structured, professional-led program, which can be delivered on an individual or group basis, in person or online.[9] However, the limited number of providers skilled in delivering psychological therapies may restrict their availability.[9]

Self-management strategies, both physical and psychological, are important aspects of chronic pain management.[9,55–56] Pain self-management is a patient-centered process involving the acquisition, practice, and execution of skills needed to respond to and manage pain and its associated symptoms. Successful and optimized pain management requires that older patients be confident and manage the everyday symptoms and consequences of pain. Identifying older patients who are already effective self-managers and those who would benefit from additional support remains a difficult area. Factors such as pain beliefs, attitudes, and motivation, also influence self-management participation.[31,60] For older patients who require additional support, various materials and interventions are available, including professional or lay-led group courses (delivered in person or online), educational resources (i.e. manuals, pamphlets, websites, videos), and self-help groups. Decisions about how best to support older patients' self-management will largely be determined by what is available and accessible to the patient locally. However, to the extent possible, older patients should be encouraged to choose between available formats, selecting individual strategies that best meet their needs.

Clinicians must discuss non-pharmacologic and self-management strategies with older patients. These strategies can improve quality of life and reduce pain and the associated impact of pain upon daily life by adopting positive pain behaviors and coping responses. Although many strategies can appear harmless, unknown risks may exist. For example, some dietary supplements or herbal remedies may pose a risk to the older patient when taken with particular pharmacologic agents.[61] It is therefore imperative that clinicians ascertain the full extent of their older patients' pain and pain management behaviors, and consider cultural, lifestyle, and socioeconomic factors that may influence these experiences.

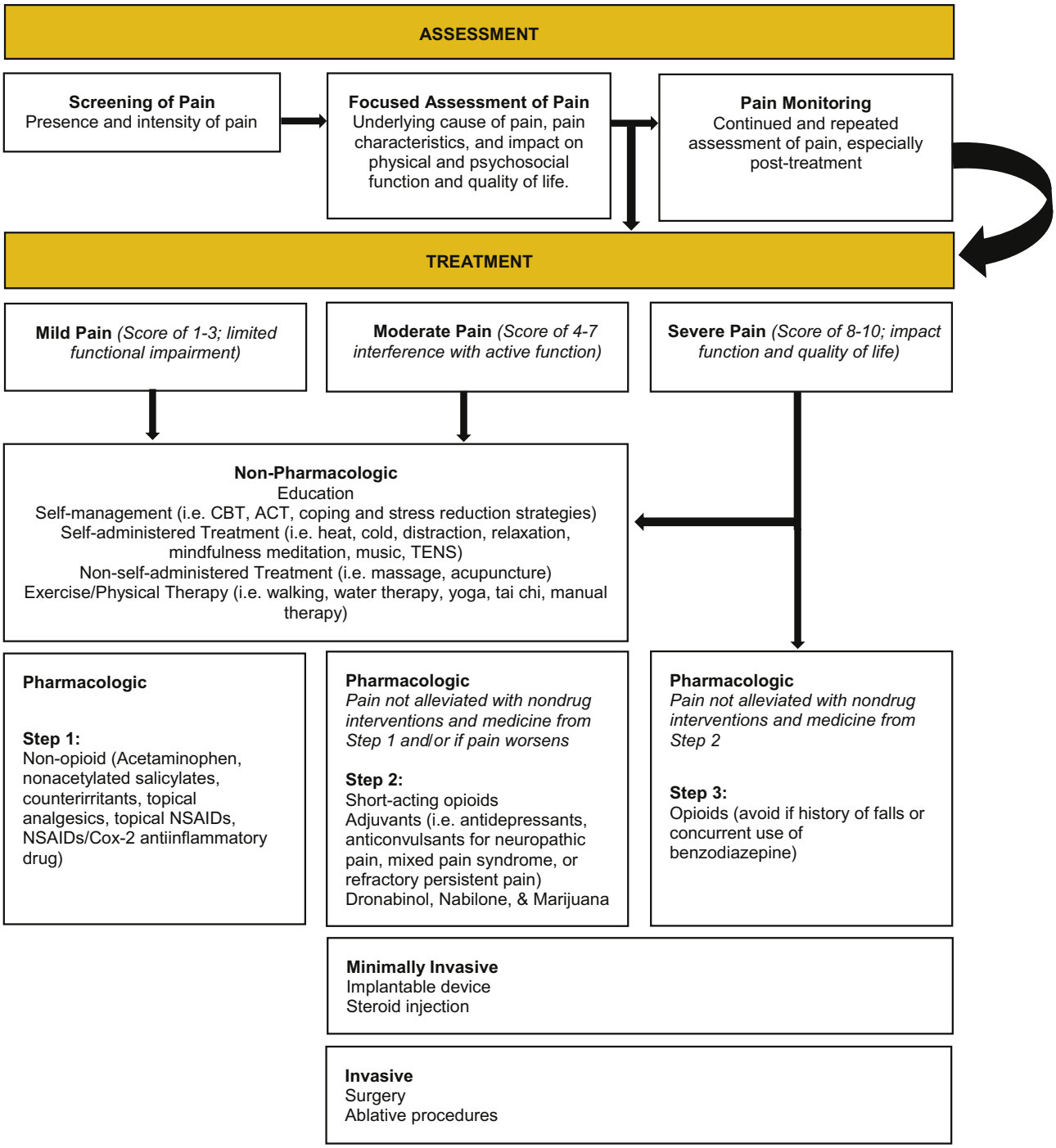
Pharmacologic Management

General principles for pharmacologic management of pain in older patients include a collaborative assessment of pain, administration of around-the-clock analgesics, frequent reassessment of the verbal, behavioral, and functional responses to treatment, and timely titration of analgesics.[62] The United States Centers for Disease Control and Prevention opioid guidelines recommend non-pharmacologic and non-opioid therapy first,[63] but implementation challenges have been raised, and analgesic medications continue to constitute the primary treatment for older adults with persistent pain.[64–65] Older persons with chronic non-cancer pain regard analgesics as an important method for managing pain, particularly when other interventions are difficult to access.[64,66] In a study of older home care adults with chronic pain in Germany, 81.4% used pain medication regularly.[67] Nonetheless, a multimodal pain management plan should be inclusive of pharmacologic medications and non-pharmacologic therapies.

Determination of the best pharmacologic approach hinges on evaluating individual characteristics and risk/benefit analyses for the options available. Age-related changes in both pharmacokinetics (alteration of absorption, distribution, metabolism, and excretion of drugs) and pharmacodynamics (drug-related adverse side effects) necessitate a modified approach to pain management in the older patient.[62,68] Renal impairment is quite common, leading to increased half-lives of medications that are excreted by the kidneys. In addition, hepatic function can decline, reducing arterial hepatic blood flow and increasing elimination time for hepatically metabolized drugs. Reductions in dose strength and frequency of analgesic dosing are necessary to decrease toxicity risk. Older age is also associated with a change in the volume of distribution. Total body fat increases while total body water decreases, translating into higher peak plasma concentrations for water-soluble drugs and prolonged half-lives for lipid soluble drugs. Lower albumin levels in frail older adults impact drugs that bind primarily to proteins.

Pharmacologic management of persistent pain in older adults is often only partially effective and limited by side effects, including urinary retention, constipation, sedation, cognitive impairment, and increased risk of falls.[69] Barriers to effective pharmacologic management of pain among older adults are diverse and include age-related physiologic changes that often dictate altering dose and frequency of analgesic administration. For many classes of pain-relieving medications, older patients may demonstrate increased analgesic sensitivity.[70] However, it is important to remember that older adults are a highly heterogeneous group, so dosing guidelines must carefully weigh a patient's pain, its' impact on their functional status, and the patient's comorbidities and other factors (e.g. polypharmacy, sociodemographic, health literacy issues). Older adults with a persistent pain disorder frequently have multiple chronic conditions (MCCs) such as diabetes, hypertension, and osteoporosis, which must be considered when formulating a treatment plan. MCCs often result in many older adults experiencing polypharmacy (defined as the use of multiple medications with five or more being a typical threshold criterion) that frequently complicates the pharmacologic management of pain.[3] Various patient sociodemographic factors can also operate as barriers. Although adequate social support enhances medication adherence,[71] many older adults live alone with limited social support.[7] In addition, many older adults cannot afford the costs of certain pain medications. Furthermore, some older adults may lack the necessary skills to read and process basic healthcare information, including understanding pill bottle instructions, information present in patient hand-outs, and clinicians' instructions about medication side effects.[72] Low health literacy can lead to problems with medication adherence, such as taking too much or too little pain medication.

Among older adults with persistent pain, commonly prescribed analgesic agents include non-opioids, opioids, and adjuvant therapies (Fig. 44.1). Issues related to the safety and efficacy of these three analgesic classes are briefly summarized.



• **Figure 44.1** Assessment and treatment approaches for pain management in older adults. (Copyright 2020 K. Herr. Used with permission K. Herr, University of Iowa, College of Nursing.)

Non-Opioids

Guidelines recommend acetaminophen as the first line agent for mild to moderate chronic pain in older adults. It is the most commonly prescribed analgesic for the treatment of mild to moderate persistent pain because of its low cost, overall safety profile, and modest efficacy.[73] Acetaminophen is an ingredient in more than 600 over-the-counter (OTC) and prescription drugs; therefore unintentional overdose can easily occur and lead to acute liver failure.[74] Unintentional overdose remains the leading cause of acetaminophen-induced hepatotoxicity as a result of treating pain.[75]

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for chronic pain in older adults when acetaminophen fails to control the pain effectively. NSAIDs are particularly helpful in treating an inflammatory type of pain where acetaminophen has limited efficacy.[76] NSAIDs continue to be one of the most commonly prescribed and consumed analgesic agents, particularly as OTC products. Although oral NSAIDs are widely considered more effective pain relievers than acetaminophen, NSAID use has

significant limitations in the form of renal, gastrointestinal, and cardiovascular toxicity, particularly among older patients. Compared with younger patients, older patients are at increased risk of experiencing gastrointestinal (GI) complications in the form of peptic ulcer disease and GI bleeding.[77] Use of either cyclooxygenase-2 (COX-2) selective inhibitor NSAIDs (e.g. celecoxib) or non-selective NSAIDs is associated with increased risk for myocardial infarction, stroke, and mortality.[78–79] Given the risks associated with oral NSAID use, increasing attention has focused on the development and testing of topical NSAIDs. Topical NSAIDs have been approved for use by the United States Food and Drug Administration, and numerous topical agents are available OTC as well.[80] A systematic review and network meta-analysis examined the relative efficacy found that topical NSAIDs were effective and safe for osteoarthritis. Diclofenac patches were the most effective topical NSAID for pain relief, while no serious gastrointestinal or renal adverse events were observed. A retrospective cohort study of patients with rheumatoid arthritis who were newly starting therapy with non-selective topical NSAIDs or oral NSAIDs found the topical NSAID group had a 36% lower risk for cardiovascular events than the oral NSAID group (hazard ratio, 0.64; 95% confidence interval 0.43–0.95).[79]

Opioids

Although well-accepted as a means of treating both acute and cancer pain, opioid analgesics remain controversial in the treatment of persistent non-cancer pain.[73] Nonetheless, opioids are considered the most powerful pain-relieving drugs available for older adults with moderate to severe persistent pain.[81] Use of opioids by older adults has increased, particularly in long term care settings where challenging pain problems exist; however, there remains limited evidence of long term effects of opioid use for chronic pain.[82] Opioids for chronic pain management in older adults may be justifiable when less potent medications have failed or are contraindicated.[83] Many older adults and healthcare providers are reluctant to use opioids because of fears of addiction and side effects, such as nausea, pruritus, constipation, drowsiness, cognitive effects, and respiratory depression.[83] Clinical monitoring and supervision are needed to manage potential side effects associated with opioids, including dry mouth, constipation, sedation, nausea, delirium, urinary retention, respiratory depression, and cognitive impairment. Other less common side effects are hypogonadism, immunosuppression, and hyperalgesia.[46] Despite these side effects, evidence from trials shows that opioid therapy for older adults can be safe and effective with appropriate cautions, including the lower starting doses, slower titration, longer dosing interval, and more frequent monitoring.[84] Still, a risk/benefit/cost analysis, along with adequate education, should be completed prior to initiating long-term opioid therapy.

Benefits may occur when clear treatment goals for opioid use are established, and patients are educated about the risks and benefits of opioid drugs.[85] According to the American Geriatrics Society's Beers Criteria 2019 Update for Potentially Inappropriate Medication Use in Older Adults, opioids should be avoided except for pain management in the setting of severe acute pain (e.g. recent fractures or joint replacement) because they may cause ataxia, impaired psychomotor function, syncope, and falls.[86] If opioids must be used, reduce simultaneous use of other central nervous system–active medications that increase risk of falls and fractures and implement strategies to reduce fall risk.[86] Further, kidney function must be closely monitored, and persons with existing kidney disease may have contraindications to morphine. Medications with codeine should be avoided. A recent systematic review demonstrated that both improvements and impairments to cognition occurred in studies with higher mean opioid doses.[87] A brief screening tool to assess cognition changes might be useful.

Opioid misuse. Opioid misuse refers to opioid use in any way not directed by a prescriber, including use without a prescription of one's own or use in greater amounts than prescribed.[88] The prevalence of opioid misuse is increasing among adults ≥65 years old, a population rapidly growing in number that requires special consideration, monitoring, and management when on opioid treatment.[89] Results from multivariable analyses among older adults visiting emergency departments suggest that the odds of opioid misuse among adults aged 65–74 years old are 6.75 times ($p < 0.001$) larger than otherwise similar adults aged 85 years and older, and the odds of opioid misuse among adults aged 75–84 years old are 2.16 times ($p < 0.001$) larger than their otherwise similar adults aged 85 years and older.[90] However, while the use of opioids under clinician supervision provides many older adults with necessary pain relief, some older adults may use opioids without a prescription, without pain, or without medical indication.[88]

Although clinicians should remain vigilant about the possibility of misuse/abuse of opioid agents among all patients irrespective of age, it is important to note that advancing age is associated with a significantly decreased risk of opioid misuse/abuse.[91] Consequently, opioid misuse may go unrecognized in older adults because of provider perceptions about older adults' behavior and the absence of efforts to screen for such misuse in this population. Older studies suggested that the underuse of opioids in older populations constitutes a bigger problem.[92] However, recent trends reveal that emergency department visits by older adults with opioid use disorder rose by 220% from 2006–2014 in the United States.[90] In Canada, the hospital admission rates from opioid overdose are higher for older adults (≥65) than younger adults.[93] Given these increases, it is important that clinicians screen for potential risk for misuse/abuse and use a valid tool such as the Opioid Risk Tool.

Adjuvant Agents

Adjuvant agents are medications administered in conjunction with analgesics to relieve pain, including anti-depressants and anti-convulsants, which are typically prescribed to treat neuropathic pain.[94] However, two Cochrane reviews did not find sufficient evidence to support the use of tricyclic anti-depressants (TCAs), such as nortriptyline and desipramine, for the treatment of chronic neuropathic pain conditions.[95,96] Although the use of low doses can mitigate side effect occurrence, many older adults experience treatment limiting anticholinergic side effects in the form of dry mouth, urinary retention, and constipation as well as an increased fall risk. Therefore the use of these medications must be considered in the context of what has been tried and the effect of pain on function; the small effects of TCAs may still be worthwhile for some older adults with severe pain. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) that has been shown to be effective in lowering pain levels among patients.[94] Patients co-prescribed an opioid were less likely to report a pain response to venlafaxine, suggesting that clinicians may wish to consider either non-opioid or alternative anti-depressant approaches to pain management in these complex patients.[97] Nausea is a commonly reported side effect with both SNRIs.

Anti-convulsant drugs such as carbamazepine are considered front line therapy for neuralgia management.[76] A particular area of concern in older adults is the risk of hyponatremia with carbamazepine because studies show that older patients with hyponatremia are more likely to have injuries from falls than those without hyponatremia. [98,99] Therefore routinely monitor sodium levels carefully with carbamazepine administration, initiated with low dosages, and slowly increased. Anti-convulsant drugs pregabalin and gabapentin have also been useful in treating neuropathic pain.[94] Side effects such as sedation, confusion, and peripheral edema can limit the use of pregabalin. Gabapentin in older patients has been associated with increased rates of falls; consequently, it is important to screen all older patients for fall risk when prescribing anti-convulsants.[98] The 2019 Beers Criteria indicates that anti-convulsants and anti-depressants, including SNRIs, may cause ataxia, impaired psychomotor function, syncope, and falls. Therefore the safety and need for these medications must be evaluated carefully and compared to their other medications to minimize increased central nervous system adverse effects.

Practice Recommendations

Here, we provide recommendations for the assessment and management of pain in older adults.

Assessment

- Identify pain-causing etiologies and perform a thorough physical exam, including any appropriate laboratory tests.
- Ask about the presence of pain, then measure its intensity and impact on function and quality of life using valid and culturally appropriate pain and function scales.
- For cognitively impaired individuals, determine ability to reliably self-report, and if impairments limit communication of pain, use a valid pain behavior tool to observe for changes as condition changes.
- Assess pain at regular intervals to establish changes in pain character (frequency, duration, triggers, and intensity) and location.

Management

- Incorporate non-pharmacologic agents to enhance relief and sense of pain control. Promote and support self-management.
- Engage older adults and any caregivers in shared treatment decision making.
- Assess and manage changing physical and cognitive abilities that can influence treatment trajectories.
- Target analgesic selection based on pain etiology and mechanism after careful individual evaluation for risks and benefits.
- If treatment goals are unmet and the patient is tolerating the therapy, consider advancing the dose before prescribing another therapy, in addition to introducing a new non-pharmacologic therapy.

Conclusion

Older adults deserve quality pain care derived from robust research, provider expertise, and patient values. Although numerous challenges and barriers exist that make assessment and treatment complex, online resources are available to guide providers, patients, and caregivers (e.g. geriatricpain.org). The goals are to detect pain early and treat it safely and effectively so that older adults can thrive and survive.

Key Points

- Evidence-based approaches to assessment and management can help older adults thrive and have a good quality of life.
- A wide range of validated tools are available to assess pain in older adults, including individuals with cognitive impairment.
- A multimodal, comprehensive approach to pain management is imperative.
- Providers need to be aware of and work to address barriers that often occur in assessing and managing pain in this age group, to physical and cognitive impairments as well as social and cultural issues.
- The full range of available pharmacologic, non-pharmacologic pain management and coping approaches should be considered.
- Providers are strongly encouraged to support older patients' efforts to become active participants in their own care.

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Managing Pain During Pregnancy and Lactation

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Use of Medications During Pregnancy

Medical management of the pregnant patient should begin with attempts to minimize the use of all medications and use nonpharmacologic therapies whenever possible. When opting for drug therapy, the clinician must consider any potential for harm to the mother or the fetus and the course of the physiologic state of pregnancy itself. The degree of protein binding and lipid solubility of the medication, speed of maternal metabolism, and molecular weight all affect the placental transfer of medications from mother to fetus. Except for large polar molecules (such as heparin and insulin) and ionized molecules (glycopyrrolate), almost all medications will reach the fetus to some degree.

Approximately 3% of newborns will have a significant congenital malformation.[1] Only 25% of fetal malformations have a known genetic cause, and only 2%–3% have a clear environmental link, such as maternal medication exposure during organogenesis.[2] One of the major limitations in evaluating any medication's potential for causing harm to a developing human fetus is the degree of species specificity for congenital disabilities. A classic example of this specificity is the drug thalidomide; nonprimate studies have revealed no teratogenic effects, but severe limb deformities occurred in human offspring when thalidomide was prescribed during pregnancy.[3]

The most critical period for minimizing maternal drug exposure is during early development, from conception through the tenth menstrual week of pregnancy (the tenth week following the last menstrual cycle). Drug exposure prior to organogenesis (prior to the fourth menstrual week) usually causes an all-or-none effect; that is, the embryo either does not survive or develops without abnormalities.[4] Drug effects later in pregnancy typically lead to single- or multiple-organ involvement, developmental syndromes, or intrauterine growth retardation.[2] Certain medications may not influence fetal organ development directly but have the potential to influence the physiology of pregnancy adversely. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) may delay the onset of labor, decrease amniotic fluid volume, or place a newborn at risk for pulmonary hypertension or renal injury.

The United States Food and Drug Administration (FDA) had developed a well known five-category labeling system for all approved drugs in the United States with pregnancy letter categories (A, B, C, D, and X). Based on available scientific and clinical evidence, this labeling system rated the potential risk for teratogenic or embryotoxic effects. In 2014 this labeling system was removed as it was determined to be confusing and did not accurately or consistently communicate differences in degrees of fetal risk. Effective 2015, a gradual process was started to remove pregnancy letter categories by June 2020. Because the risk-benefit decisions regarding the use of a drug during pregnancy are more complex than the category designations suggest, reliance on these may result in inadequately informed clinical decision making. To replace the lettering system, narrative summaries of the risk of a drug during pregnancy and discussions of the data supporting those summaries are given to provide more meaningful information to healthcare providers. Because few medications have undergone large-scale testing during human pregnancy, most medications have summaries indicating incomplete knowledge and potential for benefit and harm with drug therapy. More specifically, our present knowledge about the adverse effects of uncontrolled pain and the risks of administering medications during pregnancy remain incomplete. The physician will be left to weigh the risks against the benefits of instituting pharmacologic therapy for each individual.

Use of Medications in the Breastfeeding Mother

Many mothers are inappropriately advised to discontinue breastfeeding or avoid taking essential medications because of fears of adverse effects on their infants. This over cautious approach may be unnecessary in many cases as only a small proportion of medications are contraindicated in breastfeeding mothers or are associated with adverse effects in the infants. The same physicochemical properties that facilitate transplacental drug transfer affect drug accumulation in breast milk. High lipid solubility, low molecular weight, minimal protein binding, and the un-ionized state all facilitate the excretion of medications into breast milk. The neonatal dose of most medications obtained through breastfeeding is 1%–2% of the maternal dose.[5] Even with minimal exposure via breast milk, neonatal drug allergy and slower infant drug metabolism must be considered.[6] Only small amounts of colostrum are excreted during the first few postpartum days. Thus early breastfeeding poses little risk to the infant whose mother received medications during delivery.[7]

Most breast milk is synthesized and excreted during and immediately following breastfeeding. Taking medications after

breastfeeding or when the infant has the longest interval between feedings and avoidance of long-acting medications will minimize drug transfer via breast milk.[8] However, effective treatment of chronic pain often necessitates the use of long-acting medications, particularly long-acting opioids. To weigh the risks and benefits of breastfeeding, multiple factors should be considered: (1) the need for the drug by the mother, (2) the potential effect on milk production, (3) the amount of drug excreted in the milk, (4) the extent of absorption by the infant, (5) potential adverse effect on the infant, (6) the age of the breastfeeding child.

As with the categorical ranking of medications for use during pregnancy, the American Academy of Pediatrics (AAP) retired their grading system for the use of a drug and compatibility with breastfeeding (categories one to three). Per the FDA changes in 2015, labels now must have three headings for breastfeeding risks: risk summary, clinical considerations, and data. In a clinical report published in 2013, the AAP provides guidance to physicians regarding drug exposure and reaffirms the recommendation that most medications are safe during lactation.[9]

It is difficult for any publication to keep up with the rapidly changing information from published studies and drug approvals. Providers prescribing to the lactating mother should be familiar with a current and comprehensive database called LactMed (Drugs and Lactation Database), which can be found through the National Institute of Health.

Medications Commonly Used in Pain Management

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen

NSAIDs have both analgesic and anti-inflammatory properties and are commonly used for musculoskeletal pain.[10] Although the exact mechanism of action is uncertain, NSAIDs decrease pain by acting as non-selective inhibitors of cyclooxygenase (COX) and then inhibiting prostaglandin synthesis.[10] During pregnancy, prostaglandins modulate many key processes, including stimulation of uterine activity, maintaining patency of the fetal ductus arteriosus (essential for adequate *in utero* blood flow), and promoting fetal urine production (which contributes to the level of amniotic fluid in the second and third trimesters). As expected, alteration of prostaglandin metabolism then has varied effects on the pregnancy, depending on the timing and duration of use. For example, short-term use of indomethacin in the second trimester is effective for the treatment of pain caused by degenerating fibroids; use for long periods (more than 48 hours) in the third trimester has been associated with narrowing of the ductus arteriosus[11,12] and oligohydramnios.[13] To complicate this picture further, aspirin, the prototypical NSAID, is used in a therapeutic manner in low doses (80–160 mg/day) to decrease the incidence of pregnancy complications in certain high-risk groups but is associated with premature narrowing of the ductus arteriosus at higher doses.[14] Therefore NSAID use in pregnancy must be carefully planned to achieve the proposed benefit and avoid fetal risk. In general, if NSAID use is indicated, the duration should be short (less than 48 hours) without monitoring fetal ductus flow and amniotic fluid volume. All NSAID use for pain should be discontinued by 34 weeks of gestation to prevent pulmonary hypertension in the newborn.[15]

NSAIDs are among the most commonly used drugs during the first trimester of pregnancy.[16,17] Over the counter use of this medication is very common in this population. With their use so common, many women may not realize that there is potential for deleterious effects on them or their developing fetuses. Furthermore, as the age of first-time mothers increases, more women are likely to take NSAIDs for conditions such as joint and musculoskeletal pain. The effects of NSAID exposure on the fetus in the third trimester are well documented, associated with premature narrowing of the ductus arteriosus leading to pulmonary hypertension in the newborn. However, there is controversy as to the risk associated with maternal exposure and other congenital anomalies.[18]

There is no role for routine use of NSAIDs for pain in pregnancy other than that related to rheumatologic disease or uterine fibroids. In the largest published series of NSAID use during pregnancy to date, Ostensen and Ostensen[19] have detailed a series of 88 women with rheumatic disease, comparing the outcome in 45 who received NSAID therapy during pregnancy with 43 who were not treated during pregnancy. The most common agents used were naproxen (23/45) and ibuprofen (8/45). NSAIDs were most frequently used during the first and second trimesters because many patients stopped therapy once pregnancy was recognized. Many of the rheumatic conditions remitted later in pregnancy. They found no significant differences in pregnancy outcome (duration of pregnancy and labor, vaginal delivery rate, maternal bleeding requiring transfusion, or incidence of congenital anomalies) or the health status of offspring at long-term follow up (ranging from six months to 14 years). The authors concluded that NSAID therapy limited to periods of active rheumatic disease until weeks 34–36 did not adversely affect the neonate.[19] However, it is noted that women with rheumatic disease have poor pregnancy outcomes in general; thus these outcome data should not be applied to the general obstetric population.

More recently, Ofori and collegues[18] published a case-control study regarding the risk of congenital anomalies in pregnant users of NSAIDs. Using a population-based pregnancy registry from 1997–2003 in Quebec, they identified 93 births with congenital anomalies in 1056 women (8.8%) who filled prescriptions for NSAIDs in the first trimester of pregnancy, compared to 2478 in 35,331 (7%) women who did not. They concluded that there might be a greater risk of having children with congenital anomalies, particularly those related to cardiac septal closure.

Despite the physiologic effects of NSAIDs, the results of the Collaborative Perinatal Project have suggested that first trimester exposure to aspirin does not pose an appreciable teratogenic risk,[20] nor does ibuprofen or naproxen, the most commonly used NSAIDs. Patients who conceive while taking NSAIDs can be reassured that this will not impair pregnancy outcomes. However, NSAIDs can interfere with implantation and placental circulation. In a population-based cohort study, the risk of miscarriage was 1.8 (95% confidence interval [CI] 1.0, 3.2) with any NSAID use and was increased to 8.1 (95% CI 2.8, 23.4) if used for more than one week around the time of conception.[21]

Aspirin has well known platelet-inhibiting properties and, theoretically, may increase the risk of peripartum hemorrhage. Neonatal platelet function is inhibited for up to five days after delivery in aspirin-treated mothers.[22] Although low dose aspirin therapy (60–80 mg/day) has not been associated with maternal or neonatal complications, higher doses appear to increase the risk of intracranial hemorrhage in neonates born prior to 35 weeks of gestation.[13] Low dose aspirin has been used to improve pregnancy outcomes for women with both preeclampsia and anti-phospholipid antibodies.[23] However, as with other NSAIDs, aspirin crosses the

placenta. Although it has not been implicated in causing congenital abnormalities, it has been associated with an increased risk of vascular disruptions, particularly gastroschisis.[23,24] Data from two retrospective meta-analyses suggest that there may be a two- to three-fold increase risk of gastroschisis with aspirin exposure.[24,25] However, there are reassuring data from over 30,000 women in randomized, control trials of low dose aspirin verses placebo that have not shown any significant risk of intraventricular hemorrhage, other neonatal bleeding, or poor pregnancy outcomes.[23]

Ketorolac is an NSAID available for oral and parenteral administration. According to the manufacturer's prescribing information,[26] ketorolac did not cause congenital disabilities in the offspring of pregnant rabbits. However, ketorolac administration during labor did lead to dystocia in rodents. Ketorolac shares the platelet-inhibiting properties of other NSAIDs.[27] Although ketorolac has not undergone evaluation for its effects on the fetal ductus arteriosus or renal vasculature, it is likely to have effects similar to those of other NSAIDs. Until more information is available, it may be prudent to choose more extensively studied NSAIDs for use during pregnancy.

Based on our clinical experience and a review of the available literature, we have formulated recommendations for the use of NSAIDs during pregnancy (Box 45.1). NSAIDs use in pregnancy must be carefully planned to achieve benefit and avoid fetal risk. In general, if NSAID use is indicated, the duration should be short (48 hours) in the absence of monitoring fetal ductus flow and amniotic fluid volume. Chronic use of NSAIDs should be avoided in pregnancy, especially in the third trimester. Before the 24th week of pregnancy, the use of NSAIDs should be used with caution. It is preferable to use both low dose and short half-life NSAIDs.

Because of the anti-platelet properties of NSAIDs, many anesthesiologists are concerned about the risk of epidural hematoma formation as a result of epidural catheter placement. To date, there are no outcome studies on which to base practice recommendations. There is no evidence that low dose aspirin therapy or the use of other NSAIDs increases the risk of epidural hematoma formation following spinal or epidural placement.[28] As part of our routine history and physical examination of the parturient, we screen for any evidence of bleeding diathesis or easy bruising and, in their absence, proceed with epidural placement without further laboratory testing. This practice is consistent with the practice guidelines published by the American Society of Regional Anesthesia.[29]

Salicylic acid is excreted into breast milk in breastfeeding women, with higher doses of aspirin resulting in disproportionately higher milk concentrations. If continuous, high dose therapy is considered, an alternate drug would be preferred. With the use of daily, low dose aspirin (75 to 325 mg), no aspirin is excreted into breastmilk, and salicylate levels are low. Caution should still be exercised if more than occasional or short term aspirin use is contemplated during lactation because neonates have very slow elimination of salicylates.[30] High-dose aspirin can lead to rashes, platelet abnormalities, and bleeding in nursing infants. As for the use of NSAIDs for pain management in breastfeeding women, ibuprofen is the preferred agent because of its short half-life and safety profile for use in infants. The doses used for infants are much lower than what is excreted in breast milk. While naproxen is considered compatible with breastfeeding, other agents may be preferred because of the longer half-life. Diclofenac and indomethacin are also considered acceptable, but other agents may be preferred because of minimal data available.[31]

Little information is available on the safety of maternal ketorolac use during lactation. One study has found that ketorolac concentrations ranged from 1%–4% of maternal serum levels in breastmilk.[32] The analysis of the breast milk in 10 women given ketorolac 10 mg PO Q6 hours for four days resulted in clinically insignificant levels that the nursing infant would be exposed to.[32] Considering the bioavailability of ketorolac after oral administration, this would likely result in neonatal blood levels between 0.16% and 0.40% of the maternal dose. Ketorolac is commonly given after Cesarean section. However, the colostrum has very little excreted. The manufacturer indicates a contraindication with breastfeeding; therefore another agent should be considered 24–72 hours after birth when more breast milk is produced.

Acetaminophen is a frequently used painkiller and antipyretic drug among pregnant women. It provides similar analgesia without the anti-inflammatory effects seen with NSAIDs. Acetaminophen has no known teratogenic properties, does not inhibit prostaglandin synthesis or platelet function, and is hepatotoxic only in extreme overdosage.[13,33] As with most drugs, there are no controlled studies in pregnant women in the first trimester. In animal studies, acetaminophen has not demonstrated fetal risk. Data obtained from 88,142 patients in the Danish National Birth Cohort (1996–2003) who had information on acetaminophen use during the first trimester of pregnancy indicated that ingestion of acetaminophen during pregnancy is not related to an overall increased prevalence of congenital abnormality or an increased prevalence of the most frequent abnormalities.[34] If persistent pain demands the use of a mild analgesic during pregnancy, acetaminophen appears to be a safe and effective first-choice agent. Acetaminophen does enter breast milk, although maximal neonatal ingestion would be less than 2% of a maternal dose.[35] Acetaminophen is considered compatible with breastfeeding.[9]

• Box 45.1 Recommendations for the Use of NSAIDs During Pregnancy

- Consider non-pharmacologic management or acetaminophen use first.
- Consider the use of a mild opioid or opioid-acetaminophen combination analgesic.
- Continue aspirin or other NSAID if the symptoms cannot be controlled non-pharmacologically or with acetaminophen alone.
- Institute close fetal monitoring during the second trimester. If high doses of NSAIDs are required, periodic fetal ultrasound, including fetal echocardiography, should be used to monitor amniotic fluid volume and patency of the ductus arteriosus.
- Discontinue NSAID use after weeks 34–36 to reduce the risks of peripartum bleeding, neonatal hemorrhage, and persistent fetal circulation.

NSAID, Nonsteroidal anti-inflammatory drug.

Opioid Analgesics

Many women of childbearing age are prescribed opioids for intermittent or continual pain management. Much of our present knowledge about the effects of chronic opioid exposure during pregnancy is derived from the study of opioid-abusing patients.[36-38] Chronic opioid use in pregnancy is associated with low birth weight and decreased head circumference. However, the contribution of comorbidities, including polysubstance abuse and smoking, is not clear. Enrollment and compliance with methadone therapy for opioid dependence improves birth weight and prolongs gestation, supporting the role of therapy during gestation.[38]

Until recently, there was no evidence to suggest a relationship between exposure to any of the opioid agonists or

agonist-antagonists during pregnancy and large categories of major or minor malformations. The Collaborative Perinatal Project monitored 50,282 mother-child pairs and included exposures to codeine, propoxyphene, hydrocodone, meperidine, methadone, morphine, or oxycodone.[20] Only codeine was found to have an association with malformation (respiratory), but other studies have not confirmed this. No evidence was found for either agent to suggest a relationship to large categories of major or minor malformations. In the spring of 2011, a study by Broussard and colleagues used data gathered from the National Birth Defects Prevention Study (1997–2005), which consisted of an ongoing multi-site, population-based, case-control study of over 30 types of major structural congenital disabilities.[39] They reported that opioid treatment between one month prior to pregnancy and through the first trimester was associated with a greater risk of conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis. Codeine and hydrocodone represented 69% of all reported exposures. However, these results should be interpreted with caution, as some sample sizes were borderline, and further investigation is necessary. It is important to understand that the increased relative risk of a rare congenital disability with exposure to medications usually only translates into a modest absolute increase in risk above baseline. Healthcare providers must weigh the risks and benefits when prescribing to pregnant women or those of childbearing age.

It is important to note that there is an increased risk warning for neonatal opioid dependence when mothers are treated with opioid medications for prolonged periods during pregnancy. Abrupt cessation of opioids in the opioid dependent patient late in pregnancy can precipitate fetal withdrawal *in utero*, characterized by fetal tachycardia and fetal death.[40] Therefore pregnant women who are opioid dependent, regardless of whether the use is prescription or illicit, should not undergo acute withdrawal late in pregnancy without careful fetal monitoring. The general recommendation is to offer continuation of narcotic medication (for prescription use) or opioid substitution therapy such as methadone or buprenorphine for women using illicit drugs, with entry into treatment programs.[41-43] Additional benefits of treatment programs include improved prenatal care, higher birth weight, and reduced infectious risk to the neonate.

Neonates exposed to opioid medications *in utero* can develop dependence and manifest withdrawal symptoms in the first few days of life, known as neonatal abstinence syndrome (NAS). Characterized in mild cases by irritability and increased tone, severe neonatal withdrawal is associated with poor feeding and seizures.[44] NAS occurs in 30%–90% of infants exposed to heroin, methadone, or buprenorphine *in utero*[37,38,42,45] when mothers are treated for illicit opioid use. Patients requiring methadone to treat chronic pain tend to require lower doses of methadone, and their infants have a lower incidence of NAS, approximately 11%.[46] Most infants who have narcotic withdrawal are symptomatic by 48 hours postpartum, but there are reports of withdrawal symptoms beginning 7–14 days postpartum.[37] Neonates with prenatal exposure to opiates for long periods may require very slow weaning (as slow as a 10% reduction every third day) to prevent withdrawal symptoms.[47] The AAP considers methadone to be compatible with breastfeeding.[9]

Recognition of infants at risk for NAS and institution of appropriate supportive and medical therapy typically results in little short-term consequence to the infant.[48,49] The long-term effects of *in utero* opioid exposure are unknown. Chasnoff has considered environmental and socioeconomic factors that influence child development and concluded that no definite data exist to demonstrate long-term developmental sequelae from *in utero* opioid exposure.[50]

Buprenorphine, a partial μ-opioid agonist and κ-opioid antagonist, is currently used for office-based treatment of opioid dependence but is increasing in use for the treatment of chronic pain.[51,52] Obstetricians and anesthesiologists will encounter patients treated with buprenorphine with increasing frequency. This drug's low intrinsic receptor efficacy results in a ceiling effect and a diminished risk of overdose compared with methadone.[43] While methadone has been used for over 40 years in the treatment of opioid dependence, buprenorphine is now advocated as first line therapy.[42] The literature that reports buprenorphine in pregnancy remains limited, but buprenorphine has been found to be superior to methadone in reducing signs of withdrawal in newborns, thus requiring less medication and hospitalization time for the babies. In a randomized, double-blind trial comparing 175 women and infants treated with methadone versus buprenorphine, infants who had prenatal exposure to buprenorphine required significantly less morphine for the treatment of NAS, a significantly shorter period of NAS treatment, and significantly shorter hospitalization than those with prenatal exposure to methadone. However, there was no difference in the number of neonates requiring NAS treatment, peak NAS score, head circumference, or any other neonatal or maternal outcome.[43,53] However, in buprenorphine-maintained patients, acute pain can be challenging to treat because of the partial antagonist activity at the mu receptor. While treatment of opioid dependence requires only once-daily dosing, opioid dependent patients receiving buprenorphine with mild pain may receive analgesia simply by splitting the same daily dose into dosing intervals every 6 hours.[54]

According to the drug manufacturer insert, buprenorphine is not recommended during breastfeeding. However, it appears to be safe.[42] Because of the low levels in breast milk and the poor oral bioavailability in the infant, the infant is exposed to about 1%–1.4% of the maternal weight-adjusted dose. The risk of breast milk induced addiction appears unlikely, and there is no reason to time breastfeeding to avoid peak levels of buprenorphine. The amount of buprenorphine in the milk may not be sufficient to prevent neonatal withdrawal, and treatment of the infant may be required.[55]

Fentanyl is one of the most common parenteral opioid analgesics administered during the perioperative period. As with all opioid analgesics, administration of fentanyl to the mother immediately prior to delivery may lead to respiratory depression in the newborn.[56] Maternal administration of fentanyl or other opioids may also cause loss of the normal variability in fetal heart rate. Loss of fetal heart rate variability can signal fetal hypoxemia; thus the administration of opioids during labor may deprive obstetric caregivers of a useful tool for assessing fetal wellbeing.[57]

Meperidine undergoes extensive hepatic metabolism to normeperidine, which has a long elimination half-life (18 hours). Repeated dosing can lead to accumulation, especially in patients with renal insufficiency.[58] Normeperidine causes excitation of the central nervous system that manifests as tremors, myoclonus, and generalized seizures.[59] Significant accumulation of normeperidine is unlikely in the parturient who receives single or infrequent doses. However, meperidine offers no advantages over other parenteral opioids.

Although mixed agonist-antagonist opioid analgesic agents are widely used to provide analgesia during labor, they do not appear to offer any advantage over pure opioid agonists. In a blinded randomized comparison of meperidine and nalbuphine during labor,

the two agents appeared to provide comparable analgesic effects as well as similar neonatal Apgar and neurobehavioral scores.[60] Use of nalbuphine[61] or pentazocine[62] during pregnancy can lead to NAS. Nalbuphine may also cause a sinusoidal fetal heart rate pattern after maternal administration, thereby complicating fetal assessment.[63]

Low-affinity opioid agonists, such as tramadol (Ultram), are being used with increasing frequency, in part because of a perceived lessening of the abuse and addiction potential. There is no evidence that acute use of tramadol for labor analgesia has any advantages over more traditional opioids. According to the manufacturer's prescribing information, no drug related teratogenic effects were observed in the progeny of rats treated orally with combination tramadol and acetaminophen at 1.6 times the maximum human daily dose. However, at this dose, embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.[64] The intramuscular application of tramadol in mothers in labor reaches the neonate almost freely, confirming a high degree of placental permeability. The neonate already possesses the complete hepatic capacity for the metabolism of tramadol into its active metabolite.[65] However, the renal elimination of the active tramadol metabolite M1 is delayed, in line with the slow maturation process of renal function in neonates. Neonates born to women who are chronically receiving tramadol during pregnancy carry a risk of withdrawal. There are no studies on the relative rates of NAS comparing tramadol with other opioid analgesics.

Postoperative analgesia for most pregnant women undergoing non-obstetric surgery can be readily provided using narcotic analgesics (Tables 45.1 and 45.2). Fentanyl, morphine, and hydromorphone are all safe and effective alternatives when a potent opioid is needed for parenteral administration. There are a range of safe and effective oral analgesics. For mild pain, acetaminophen alone or in combination with hydrocodone is a good alternative. For moderate pain, oxycodone alone or in combination with acetaminophen is effective. More severe pain may require morphine or hydromorphone, both of which are available for oral administration.

Narcotic analgesics can also be administered into the intrathecal or epidural compartments to provide postoperative analgesia. Such neuraxial administration of hydrophilic agents, e.g. morphine, greatly reduces total postoperative opioid requirements while providing excellent analgesia.[66] Spinal or epidural delivery of opioids can be used to minimize maternal plasma concentrations, thereby reducing placental transfer to the fetus or exposure of the breastfeeding infant.

Maternal use of opioids can result in infant drowsiness, central nervous depression, and even death. Opioids are excreted into breast milk. Pharmacokinetic analysis has demonstrated that breast milk concentrations of codeine and morphine are equal to or somewhat higher than maternal plasma concentrations.[67] Meperidine use in breastfeeding mothers via patient-controlled analgesia (PCA) has resulted in significantly greater neurobehavioral depression of the breastfeeding newborn than equianalgesic doses of morphine.[68] After absorption from the infant's gastrointestinal tract, opioids contained in ingested breast milk undergo significant first-pass hepatic metabolism. Morphine undergoes glucuronidation to inactive metabolites.[67] Meperidine undergoes *N*-demethylation to the active metabolite normeperidine.[69] Normeperidine's half-life is markedly prolonged in the newborn,[70] so that regular breastfeeding leads to accumulation and the resultant risks of neurobehavioral depression and seizures. The AAP considers the use of many opioid analgesics, including codeine, fentanyl, methadone, morphine, and propoxyphene, to be compatible with breastfeeding.[9] There are insufficient data to determine the safety of buprenorphine with breastfeeding. However, the excretion of buprenorphine into breast milk is minimal.[71]

TABLE 45.1 Oral Analgesics for Treating Pain During Pregnancy*

Drug	How Supplied	Equianalgesic Oral Dose (Equianalgesic Oral Dose) (mg)
Acetaminophen	—	325, 500, 625 mg tabs; 500 mg/15 mL elixir
Codeine	60	15, 30, 60 mg tabs; 15 mg/5 mL elixir
Acetaminophen with codeine	—	300 • 15,300 • 30, 300 • 60 mg tabs; 120 • 12/5 mL elixir
Hydrocodone	60	—‡
Acetaminophen with hydrocodone	—	500 • 2.5, 500 • 5, 500 • 7.5, 660 • 10 mg tabs; 500 • 7.5/15 mL elixir
Oxycodone	10	5 mg tabs; 5 mg/5 mL elixir
Acetaminophen with oxycodone	—	325 • 5, 500 • 5 mg tabs; 325 • 5/5 mL elixir
Morphine	20	15, 30 mg tabs; 10, 20 mg/5 mL elixir
Hydromorphone	2	2, 4, 8 mg tabs; 5 mg/5 mL elixir

*There is wide variability in the duration of analgesic action from patient to patient. All the oral agents listed are generally started with dosing every 4–6 hours. The dosing interval can then be adjusted as needed to maintain adequate analgesia.

‡There is no oral formulation of hydrocodone alone available in the United States.

TABLE 45.2 Analgesics for Moderate to Severe Pain During Pregnancy*

Drug	Equianalgesic Parenteral Dose	Equianalgesic Oral Dose
Fentanyl	50 µg	—
Hydromorphone	1 mg	2–4 mg
Morphine	5 mg	30–60 mg
Meperidine	50 mg	150–300 mg

*There is wide variability in the duration of analgesic action from patient to patient. All the parenteral agents listed are generally started with parenteral dosing every 3–4 h and the oral agents every 4–6 h. The dosing interval can then be adjusted as needed to maintain adequate analgesia.

Local Anesthetics

Few studies have focused on the potential teratogenicity of local anesthetics. Lidocaine and bupivacaine do not appear to pose a significant developmental risk to the fetus. In the Collaborative Perinatal Project,[20] only mepivacaine had any suggestion of teratogenicity. However, the number of patient exposures was inadequate to draw conclusions. Animal studies have found that continuous exposure to lidocaine throughout pregnancy does not cause congenital anomalies but may decrease neonatal birth weight.[72] Continuous exposure to local anesthetics is unusual but might be seen with the frequent use of local anesthetic patches or creams, which are used for postherpetic neuralgia and other neuropathic pain states.

Neither lidocaine nor bupivacaine appear in measurable quantities in breast milk after epidural local anesthetic administration during labor.[7] Intravenous infusion of high doses (2–4 mg/min) of lidocaine to suppress cardiac arrhythmias has led to minimal levels in breast milk.[73] Based on these observations, continuous epidural infusion of dilute local anesthetic solutions for postoperative analgesia should result in only small quantities of drug reaching the fetus. The AAP considers local anesthetics to be safe for use in the nursing mother.[9]

Mexiletine is an orally active antiarrhythmic agent with structural and pharmacologic properties similar to those of lidocaine. This agent has shown promise in the treatment of neuropathic pain. Mexiletine is lipid-soluble and freely crosses the placenta. There are no controlled studies in humans of mexiletine use during pregnancy. However, studies in rats, mice, and rabbits using doses up to four times the maximum daily dose in humans have demonstrated an increased risk of fetal resorption but not teratogenicity.[74] Mexiletine appears to be concentrated in breast milk. However, based on expected breast milk concentrations and average daily intake of breast milk, the infant would receive only a small fraction of the usual pediatric maintenance dose of mexiletine.[75] The AAP considers mexiletine use to be compatible with breastfeeding.[9]

Steroids

Corticosteroids may be used commonly in pregnancy in patients with autoimmune disease and those with premature rupture of membranes. There is variability in placental metabolism and transplacental passage of steroids depending on the preparation.[10] Most corticosteroids cross the placenta, although prednisone and prednisolone are inactivated by the placenta,[2] while dexamethasone and betamethasone do not undergo significant metabolism.[10] Fetal serum concentrations of prednisone are less than 10% of maternal levels. No increase in malformations was seen among 145 patients exposed to corticosteroids during their first trimester of pregnancy.[20] The use of corticosteroids during a limited trial of epidural steroid therapy in the pregnant patient probably poses a minimal fetal risk (see further discussion later in this chapter).

In breastfeeding mothers, less than 1% of a maternal prednisone dose appears in the nursing infant over the next three days.[76] This amount of steroid exposure is unlikely to affect infant endogenous cortisol secretion.[76]

Benzodiazepines

Benzodiazepines are among the most frequently prescribed drugs and are often used as anxiolytic agents to treat insomnia and as skeletal muscle relaxants in patients with chronic pain.[77] First trimester exposure to benzodiazepines may be associated with an increased risk of congenital malformations. Diazepam may be associated with cleft lip or cleft palate,[78] and with congenital inguinal hernia.[79] However, epidemiologic evidence has not confirmed the association of diazepam with cleft abnormalities. The incidence of cleft lip and palate remained stable after the introduction and widespread use of diazepam.[80] Epidemiologic studies have confirmed the association of diazepam use during pregnancy with congenital inguinal hernia.[80] Benzodiazepine use immediately before delivery also increases the risk of fetal hypothermia, hyperbilirubinemia, and respiratory depression.[81]

Two other benzodiazepines have been evaluated for teratogenicity. Chlordiazepoxide has been reported to produce a four-fold increase in congenital anomalies, including spastic diplegia, duodenal atresia, and congenital heart disease.[82,83] However, a study of over 200,000 Michigan Medicaid recipients did not support these earlier findings.[84] Instead, this study found a high co-prevalence of alcohol and illicit drug use in patients receiving benzodiazepines. Benzodiazepine use alone did not appear to be a risk factor for congenital anomalies. Oxazepam use during pregnancy has also been associated with congenital anomalies, including a syndrome of dysmorphic facial features and central nervous system defects.[85] In addition to the risks of teratogenesis, neonates who are exposed to benzodiazepines *in utero* may experience withdrawal symptoms immediately after birth.[86]

Diazepam and its metabolite desmethyldiazepam in the breastfeeding mother can be detected in the infant's serum for up to 10 days after a single maternal dose. This is caused by the slower metabolism in neonates than in adults.[87] Clinically, infants who are nursing from mothers receiving diazepam may show sedation and poor feeding.[87] It appears most prudent to avoid any use of benzodiazepines during organogenesis, near the time of delivery, and during lactation.

Anti-depressants

Anti-depressants are often used in the management of migraine headaches, as well as for analgesic and anti-depressant purposes in chronic pain states. Selective serotonin reuptake inhibitors (SSRIs) have become the mainstay for the treatment of depression and are widely prescribed. As with most medications, increased use has been associated with increased reports of adverse effects in pregnancy and neonates. Although initially thought to be safe in early pregnancy, unpublished epidemiologic reports from GlaxoSmithKline have raised concern that paroxetine, one of the most widely prescribed anti-depressants, may be associated with an increase in malformations when used in the first trimester, particularly cardiovascular malformations.[88] This recent retrospective epidemiologic study of 3581 pregnant women exposed to paroxetine or other anti-depressants during the first trimester has suggested an increased risk of overall major congenital malformations for paroxetine than other anti-depressants (odds ratio [OR], 2.20; 95% CI, 1.34–3.63). There was also an increased risk for cardiovascular malformations with the use of paroxetine than other anti-depressants (OR, 2.08; 95% CI, 1.03–4.23); 10 out of 14 infants with cardiovascular malformations had ventricular septal defects. Use late in pregnancy has also recently become a concern, with reports of NAS, including jitteriness or seizures,[89] and pulmonary hypertension in the newborn.[90] While paroxetine is generally discouraged in pregnancy, citalopram, and sertraline are considered an option and have not been associated with congenital disabilities. It is important to note that although the relative risk of adverse outcomes has increased, the incidence of malformations (1%–3%)

and pulmonary hypertension (0.5%–1%) remain low, whereas the presence of severe depression in pregnant women is high (15%). As with all medications, the risk of no medication must be carefully weighed against the risk of treatment. Many women will need to remain on anti-depressants throughout pregnancy, and the low incidence of adverse outcomes remains reassuring.

Although tricyclic anti-depressants have had a more limited role in the treatment of depression, they can be of benefit in patients with chronic pain.[91] Amitriptyline is teratogenic in hamsters (encephaloceles) and rats (skeletal defects).[13] Imipramine has been associated with several congenital disabilities in rabbits but not in rats, mice, or monkeys.[92] Although there have been case reports of human neonatal limb deformities after maternal amitriptyline and imipramine use, large human population studies have not revealed association with any congenital malformation, with the possible exception of cardiovascular defects after maternal imipramine use.[13] There have been no reports linking maternal desipramine use with congenital disabilities. Withdrawal syndromes have been reported in neonates born to mothers using nortriptyline, imipramine, and desipramine, with symptoms including irritability, colic, tachypnea, and urinary retention.[13]

Amitriptyline, nortriptyline, and desipramine are all excreted into human milk. Pharmacokinetic modeling has suggested that infants are exposed to about 1% of the maternal dose.[93] In a critical review of the literature regarding the use of anti-depressants during breastfeeding, Wisner and colleagues have concluded that amitriptyline, nortriptyline, desipramine, clomipramine, and sertraline are not found in quantifiable amounts in nurslings and reported no adverse effects. They recommended the use of these agents as the anti-depressants of choice for breastfeeding women.[93] Fluoxetine is also excreted into human milk and has a milk-to-plasma ratio of about 0.3. No controlled studies are available to guide fluoxetine therapy during lactation.[13] However, colic and high infant serum levels have been reported.[94] Maternal doxepin use has also been associated with elevated plasma levels of the metabolite *N*-desmethyldoxepin and respiratory depression in a nursing infant.[95] The AAP considers all anti-depressants to have unknown risk during lactation.[9]

Duloxetine, a selective norepinephrine reuptake inhibitor (SNRI), is representative of a new class of drug that combines inhibition of serotonin and norepinephrine reuptake. Duloxetine is efficacious for depression and neuropathic pain and may have particular efficacy in diabetic neuropathy. Neonates born to mothers receiving SSRI or SNRI drugs may have a withdrawal reaction, as discussed earlier. Although the relative risks and benefits of breastfeeding when a woman is receiving duloxetine have not been fully evaluated, the manufacturer advises against its use during breastfeeding.

Anti-convulsants

Several anti-convulsant medications are used in chronic pain management. However, most data regarding the fetal risk of major malformation in women taking anti-convulsants are derived from the treatment of epilepsy. Although epilepsy itself is not associated with an increased risk of congenital malformations, some theoretical risk may exist. Despite this, data from anti-convulsant use in epileptic women is used to assess the risk of the same medications when used for pain conditions. The American Academy of Neurology and American Epilepsy Society subcommittee recently undertook a systematic review of the evidence for teratogenic potential and perinatal outcomes among pregnant women on antiepileptic medication.[96,97] The review found that valproic acid exposure, especially in the first trimester, contributes to neural tube defects, facial cleft, and possibly hypospadias. They also found that neonates of women taking anti-convulsants were also more likely to be small for gestational age and have lower Apgar scores. Treatment with valproic acid is more likely to be associated with major congenital malformation than treatment with carbamazepine or lamotrigine. There is a possible dose relationship for the development of congenital malformations for valproic acid during the first trimester. Though not consistent throughout all studies, a valproic acid dose of greater than 1000 mg daily may be associated with the greatest risk of malformations.

In the same review, carbamazepine was associated with an increased risk of cleft palate, but this was not confirmed by another study focusing specifically on carbamazepine using the European Surveillance of Congenital Anomalies (EUROCAT) database. Though this study did not find an association between carbamazepine and clefts, it did find an association with spina bifida.

Data suggests that topiramate (Topamax) and its generic version increase the risk of cleft lip and cleft palate in babies born to women who use the medication during pregnancy.[98] Its use has also been linked to low birth weight.[99]

Gabapentin is an anti-convulsant that is being used for the treatment of neuropathic pain syndromes. Little information exists about the safety of gabapentin in pregnant women, and thus far, the Gabapentin Registry Study does not show an increased risk for adverse maternal and felt events.[100] In their prescribing information, the manufacturer[101] has reported a series of nine women who received gabapentin during their pregnancies. Four women elected pregnancy termination, four had normal outcomes, and one neonate had pyloric stenosis and an inguinal hernia. Insufficient data exist to counsel patients regarding the fetal risk of gabapentin use during pregnancy.

A drug similar to gabapentin is pregabalin, which combines anti-convulsant activity and affinity to the γ-aminobutyric acid receptor. The main applications of pregabalin are for the treatment of pain associated with diabetic neuropathy and postherpetic neuralgia.

Patients contemplating childbearing who are receiving anti-convulsants should have their pharmacologic therapy critically evaluated. Those taking anti-convulsants for neuropathic pain should strongly consider discontinuation during pregnancy, particularly during the first trimester. Consultation with a perinatologist is recommended if continued use of anti-convulsants during pregnancy is being considered. Frequent monitoring of serum anti-convulsant levels and folate supplementation should be initiated, and maternal α-fetoprotein screening may be considered to detect fetal neural tube defects.

The use of anti-convulsants during lactation does not seem to be harmful to infants. Phenytoin, carbamazepine, and valproic acid appear in small amounts in breast milk, but no adverse effects have been noted.[13] There are limited data on both pregabalin and gabapentin.

Ergot Alkaloids

Ergotamine can have significant therapeutic efficacy for the episodic treatment of migraine headaches. However, even low doses of ergotamine are associated with significant teratogenic risk, and higher doses have caused uterine contractions and spontaneous abortion.[91] During lactation, ergot alkaloids are associated with neonatal convulsions and severe gastrointestinal disturbances.[13] Occasionally, methyl-ergonovine is systemically administered to treat uterine atony and maternal hemorrhage immediately after delivery. This brief exposure does not contraindicate breastfeeding.[102]

Caffeine

Caffeine is a methylxanthine often used in combination with analgesics for the management of vascular headaches. It is readily absorbed from the gastrointestinal (GI) tract and crosses the placenta such that concentrations in the fetus are similar to maternal plasma levels.[103] Early studies of caffeine ingestion during pregnancy suggested an increased risk of intrauterine growth retardation, fetal demise, and premature labor,[104] while more recent studies do not.[105] Although the data are not strongly compelling against caffeine use in pregnancy, most obstetricians recommend that pregnant women limit caffeine intake to less than 300 mg per day. To date, there is no evidence for congenital disabilities related to caffeine.[106]

Caffeine use is also associated with certain cardiovascular changes. Ingestion of modest doses of caffeine (100 mg/m^2, a dose similar to that found in two cups of brewed coffee) in caffeine-naïve subjects produces modest cardiovascular changes in mother and fetus, including increased maternal heart rate and mean arterial pressure, increased peak aortic flow velocities, and decreased fetal heart rate.[107] The modest decrease in fetal heart rate and increased frequency of fetal heart rate accelerations may confound the interpretation of fetal heart tracings. Caffeine ingestion is also associated with an increased incidence of tachyarrhythmia in the newborn, including supraventricular tachyarrhythmias, atrial flutter, and premature atrial contractions.[108] Many over-the-counter analgesic formulations contain caffeine (typically in amounts from 30–65 mg/dose), and the use of these preparations must be considered when determining total caffeine exposure.

Moderate ingestion of caffeine during lactation (up to two cups of coffee/day) does not appear to affect the infant. Breast milk usually contains less than 1% of the maternal dose of caffeine, with peak breast milk levels appearing 1 hour after maternal ingestion. Excessive caffeine use may cause increased wakefulness and irritability in the infant.

Sumatriptan

Sumatriptan is a selective serotonin agonist that has achieved widespread use because of its efficacy in the treatment of migraine headaches. It has been associated with fetal malformations in rabbits but not in rats.[109] Limited data in humans have not demonstrated any strong teratogenic effects.[91,110] Sumatriptan is advantageous in the treatment of migraine headache in pregnancy because it does not share uterine contractile properties with ergotamine and would not likely have abortifacient effects.[111] Beginning in January 1996, Glaxo Welcome established a registry to prospectively evaluate the risk of sumatriptan use during pregnancy.[112] The accumulated evidence from sumatriptan's pregnancy registry and other studies suggest that this drug is a safe therapeutic option for the treatment of migraine attacks in pregnant women.

A minimal amount of sumatriptan is excreted into breast milk, and it is considered safe in breastfeeding. The use of sumatriptan during lactation has not been well studied. One study of a single 6 mg dose of subcutaneous sumatriptan given to lactating women found total breast milk sumatriptan to be only 0.24% of the maternal dose. Because sumatriptan is poorly absorbed from the infant GI tract, only 14% of the drug ingested by the fetus would be bioavailable. Even this minor exposure could be largely avoided by expressing and discarding all milk for 8 h after injection.[113]

β-Blockers

Propranolol and other β-blockers are used for chronic prophylaxis against migraine and non-migraine vascular headaches. Most of the studies on β-blocker use during pregnancy involve women being treated for hypertension instead of migraine prophylaxis, and hypertension itself may increase the risk for SGA.[114] A 2009 Cochrane review looking at β-blocker use for mild to moderate hypertension during pregnancy found that the effect of β-blockers on the perinatal outcome is unclear.[115] There is no evidence that propranolol is teratogenic. Fetal effects noted with maternal consumption of propranolol include decreased weight, potentially because of a modest decrease in maternal cardiac output, with consequent diminished placental perfusion.[116] Patients should be aware that fetal toxicity can result in complications, including intrauterine growth retardation, hypoglycemia, bradycardia, and respiratory depression.[116] Longer acting agents should lead to less fluctuation in maternal and fetal blood concentrations and perhaps less fluctuation in the drug effects on fetal heart rate. In the lactating mother, propranolol doses of up to 240 mg/day appear to have minimal neonatal effects, resulting in subtherapeutic exposure to the infant.

Marijuana

Marijuana is the most commonly used dependent substance in pregnancy.[117] This is likely because of increased use in the generalized population for medical and recreational use and de-stigmatization of the substance. California first made marijuana legal in 1996, and its use in the United States has steadily increased since that time. At the time of writing this chapter, 33 states and the District of Columbia have medical cannabis programs, 11 states have legalized recreational use, and another 16 states have decriminalized. This increase in legalization has also increased the perception of safety, although the chemical concentration of tetrahydrocannabinol (THC) has increased dramatically. While the potency of THC was about 4% on average in marijuana in 1995, it has increased to about 12% now. Over a similar time frame, the number of women of reproductive age who believe there is no risk to regular marijuana use has increased from 4.6%–19%.[118]

The American College of Obstetricians and Gynecologists[118] and the Centers for Disease Control[117] currently recommend that all pregnant women are screened for the use of marijuana and encouraged to discontinue use during pregnancy. It is known that THC does cross the placenta and into breast milk, resulting in fetal and neonatal exposure. There is a limitation of evidence for outcomes with marijuana use during pregnancy and breastfeeding as most of the studies are retrospective and based on patient self-reporting, likely leading to underreporting. Additionally, many studies do not adjust for confounding factors such as tobacco use and socioeconomic status. However, there is enough human and animal data to suggest potential harm with the use of cannabis. Marijuana use may be associated with long-term adverse neurobehavioral outcomes, preterm birth, stillbirth, growth restriction, and neonatal intensive care admissions. Therefore women should be educated to refrain from marijuana use during pregnancy and lactation.[118]

Evaluation and Treatment of Pain During Pregnancy

Pain medicine specialists may be asked to consult on patients with uncontrolled pain during the course of pregnancy. Often, severe pain can arise from an extreme form of one of the more common

musculoskeletal pain syndromes of pregnancy, including abdominal wall and ligamentous pain, hip pain, and pelvic girdle pain. Thus working knowledge of the painful musculoskeletal conditions that occur during pregnancy is essential. Low back pain and migraine headaches are very common and will be discussed during pregnancy because these are among the most common problems encountered in practice. Finally, although sickle cell pain crisis is less common, it provides a good example of the approach to managing chronic recurrent pain during the course of pregnancy and will be discussed below

Musculoskeletal Considerations in Pregnancy

Abdominal Wall and Ligamentous Pain

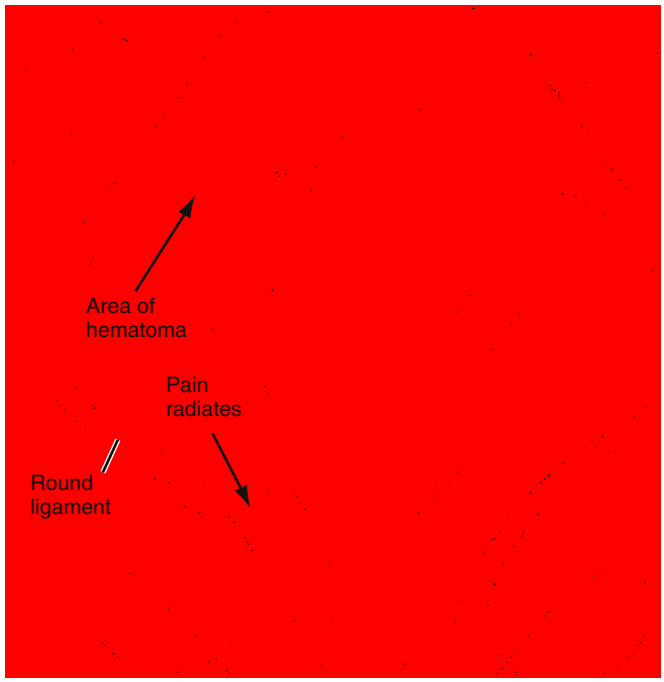
Abdominal wall pain during pregnancy typically results in prompt evaluation by an obstetrician. One of the most common causes of abdominal pain early in pregnancy is miscarriage, which presents with abdominal pain and vaginal bleeding. Unruptured ectopic pregnancy and ovarian torsion may present with vague hypogastric pain and suprapubic tenderness. Once these conditions requiring the immediate attention of an obstetrician have been ruled out, myofascial causes of abdominal pain should be considered.

The round ligaments stretch as the uterus rises in the abdomen. If the pull is too rapid, small hematomas may develop in the ligaments (Fig. 45.1). This usually begins at 16–20 weeks of gestation, with pain and tenderness localized over the round ligament, which radiates to the pubic tubercle.[119] Treatment is bed rest and local warmth, along with oral analgesics in more severe cases.

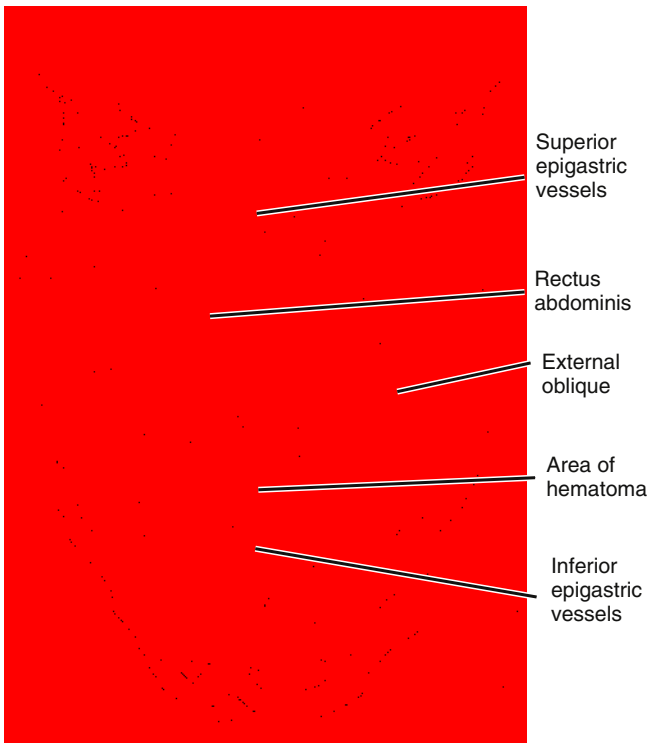
Less common is abdominal pain arising from hematoma formation within the sheath of the rectus abdominis muscle (Fig. 45.2). As the uterus expands, the muscles of the abdominal wall become greatly overstretched. Rarely, the rectus muscle may dehisce, or the inferior epigastric veins rupture behind the muscle. Severe pain localized to a single segment of the muscle often follows a bout of sneezing. Diagnosis of rectus hematoma is made when localized pain is exacerbated by tightening the abdominal muscles (raising the head in the supine position). Ultrasonography can help confirm the diagnosis. Conservative management with bed rest, local heat, and mild analgesics are often all that is needed.

Hip Pain

Two relatively rare conditions, osteonecrosis and transient osteoporosis of the hip, occur with somewhat greater frequency during pregnancy.[120] Although the exact cause is unknown, high levels of estrogen and progesterone in the maternal circulation and increased interosseous pressure may contribute to the development of osteonecrosis.[121] Transient osteoporosis of the hip is a rare disorder characterized by pain and limitation of motion of the hip and osteopenia of the femoral head.[122] Both conditions present with hip pain during the third trimester, which may be sudden or gradual in onset. Osteoporosis is easily identified, with plain radiography demonstrating osteopenia of the femoral head and preservation of the joint space. Osteonecrosis is best evaluated with magnetic resonance imaging (MRI), which will demonstrate changes before they appear on plain radiographs. Both conditions are managed symptomatically during pregnancy. Limited weight bearing is essential in transient osteoporosis of the hip to avoid fracture of the femoral neck.[122]



• **Figure 45.1** Abdominal pain arising from stretch and hematoma formation in the round ligament usually presents between 16 and 20 weeks of gestation, with pain and tenderness over the round ligament, which radiates to the pubic symphysis. (Adapted with permission from Chamberlain G. ABC of antenatal care. Abdominal pain in pregnancy. *Br Med J.* 1991;302:1390–1394.)



• **Figure 45.2** Stretch of the abdominal wall in pregnancy can tear the rectus abdominis muscle or inferior epigastric veins and form a painful hematoma within the rectus sheath. Pain is well localized and can be severe, often starting after a bout of coughing or sneezing. (Adapted with permission from Chamberlain G. ABC of antenatal care. Abdominal pain in pregnancy. *Br Med J.* 1991;302:1390–1394.)

• Box 45.2 Signs and Symptoms of the Syndrome of "Pelvic Girdle Pain"

- A history of time- and weight-bearing–related pain in the posterior pelvis, deep to the gluteal area
- A positive "posterior pelvic provocation test" (Fig. 45.5)
- A pain drawing with well defined markings of stabbing pain in the buttocks distal and lateral to the L5–S1 area, with or without radiation to the posterior thigh or knee, but not into the foot (Fig. 45.6)
- Free movements in the hips and spine and no nerve root symptoms
- Pain when turning in bed

Adapted with permission from Ostgaard HC, Zetherström G, Roos-Hanson E, et al. Reduction of back and posterior pelvic pain in pregnancy. *Spine*.1994;19:894–900.

Pelvic Girdle Pain

Causative Factors and Clinical Presentation

Pelvic girdle pain (PGP) is a clinical syndrome with pain localized from the posterior iliac crest and gluteal fold over the anterior and posterior elements of the bony pelvis. Many other terms have described the syndrome, including symphysis pubis dysfunction, pelvic joint insufficiency, pelvic girdle relaxation, and posterior pelvic pain.[123] This pain entity is distinct from pregnancy related low back pain (Box 45.2). Pain is often described as stabbing, sometimes burning in the region of the sacroiliac joints, and can extend anteriorly to the region of pubic symphysis. Radiation patterns can include the groin, perineum, and posterior thigh in a non-dermatomal pattern. The location of pain can change during the course of pregnancy. Onset can be from the first trimester to one month postpartum, though most regard the third trimester as the peak of symptoms. In most patients, symptoms subside by six months postpartum. The incidence is difficult to establish given various diagnostic criteria used. Some report the incidence to be between 16% and 25%.[124,125]

The cause of PGP remains unclear but is likely multifactorial with mechanical, hormonal, and genetic influences. Mechanical factors relate to the separation of the pubic symphysis during pregnancy. Hormonal changes include elevated levels of progesterone and relaxin. Genetic influence is based on epidemiologic findings of increased prevalence among first-degree relatives.

Back Pain

Causative Factors and Clinical Presentation

Pregnancy related low back pain (PLBP) is characterized as pain in the lumbar region. Fifty percent of women will experience low back pain during pregnancy, which is commonly looked upon as a normal part of pregnancy (Fig. 45.3).[126] In one-third of pregnant women, back pain is a severe problem that compromises everyday activity.[127] The pain resembles the low back pain of the nonpregnant state and is often described as dull and aching in nature. There can be a limitation to the range of motion of the lumbar spine, and the pain is exacerbated by both forward flexion and palpation of the erector spinae muscles.[128]

As with PGP, the cause of PLBP is likely multifactorial. To balance the anterior weight of the womb, the lumbar lordosis becomes markedly accentuated during pregnancy and may represent a mechanical cause for the pain.[129] Endocrine changes during pregnancy may also play a role in the development of back pain. Relaxin, a polypeptide secreted by the corpus luteum, softens the ligaments around the pelvic joints and cervix, accommodating the developing fetus and facilitating vaginal delivery. This laxity may cause pain by allowing an exaggerated range of motion.[130]

The onset of low back pain is usually around the 18th week of pregnancy, with the peak intensity between the 24th and 36th weeks.[128] However, the pain can start as early as the first trimester or as late as three weeks postpartum. Sixteen percent of women with PLBP report persistent pain six years later, thus representing pregnancy as a risk factor for persistent low back pain.[131] Although radicular symptoms often accompany low back pain during pregnancy, herniated nucleus pulposus (HNP) only has an incidence of 1:10,000.[132] Pregnant women do not have an increased prevalence of lumbar disc abnormalities.[133] Direct pressure of the fetus on the lumbosacral nerves or lumbar plexus has been postulated as the cause of radicular symptoms.

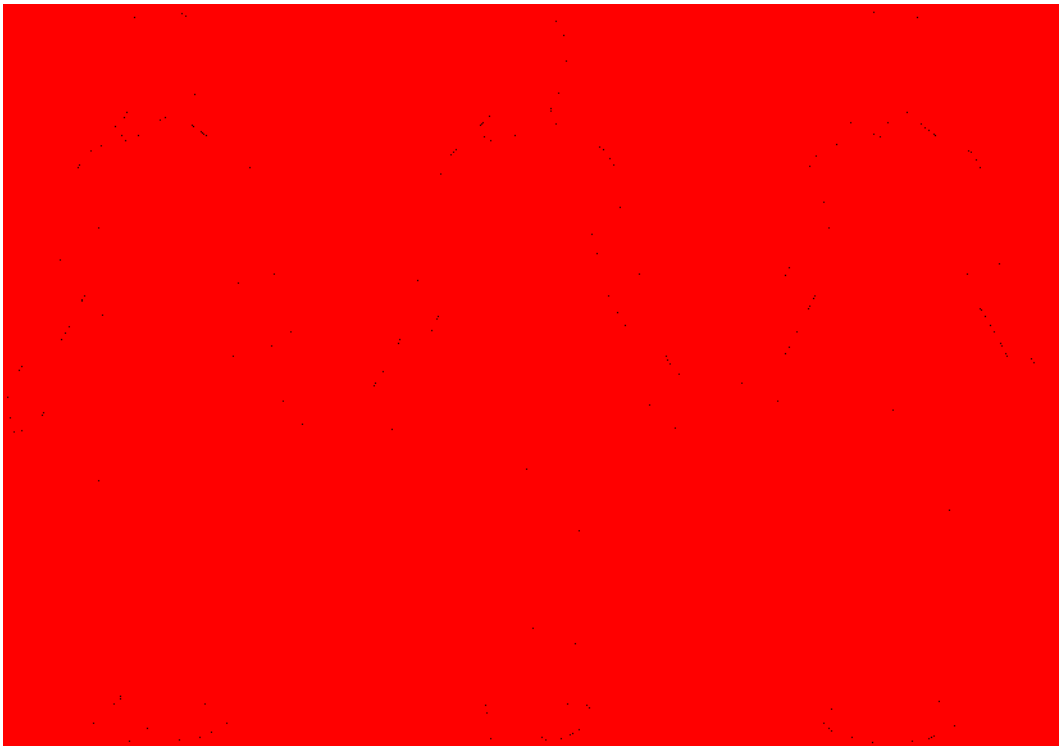
Evaluation of the Patient With Back and Pelvic Girdle Pain

Evaluation of the pregnant patient with low back pain and PGP must begin with a thorough history and physical examination.[134] The aim is to exclude other causes of pain as obstetric complications (preterm labor, abruption, degeneration of uterine fibroids, round ligament pain, and chorioamnionitis) may also present with low back pain.[135,136] Urologic disorders, including hydronephrosis, pyelonephritis, and renal calculi, may also present with low back discomfort.[137] Major morphologic changes occur in the collecting system of pregnant women, including dilation of the calices, renal pelvis, and ureters (Fig. 45.4).[138] The physical examination should include complete back and neurologic evaluations. Particular attention should be directed toward the pelvis and sacroiliac joints during the examination. Posterior pelvic pain (sacroiliac dysfunction) can often be distinguished from other causes of low back pain based on physical examination (Figs. 45.5 and 45.6; Table 45.3; Box 45.2). During the physical examination, positive straight leg raise (typical low back pain with or without radiation to the ipsilateral lower extremity) is consistent with sacroiliac subluxation or HNP. Unilateral loss of knee or ankle reflex or the presence of a sensory or motor deficit is suggestive of lumbar nerve root compression.

X-ray imaging techniques such as computed tomography are not ideal in pregnancy. However, pregnancy is not an absolute contraindication to radiographic evaluation. Radiation exposure during pregnancy leads to concerns about resultant congenital anomalies, mental retardation, and increased risk of subsequent cancers.[139] No detectable growth or mental abnormalities have been associated with fetal exposure to less than 10 rad; the dose received during a typical three-view spinal series typically does not exceed 1.5 rad.[140] Plain radiographs will contribute vital information primarily when fracture, dislocation, and destructive lesions of the bone are suspected.

MRI has revolutionized diagnostic imaging during pregnancy, proving effective and reliable in the diagnosis of many structural abnormalities.[141] Although MRI appears to be safe during pregnancy, there are no long-term studies examining the safety of fetal exposure to intense magnetic fields during gestation.[142] Schwartz[140] has presented a thorough and insightful review of neurodiagnostic imaging of the pregnant patient. Practical guidelines for the use of radiographic studies in the evaluation of pregnant patients are given in Box 45.3.

Electromyography and nerve conduction studies (collectively referred to as EMG) serve as good screening tests in patients with new onset of low back pain accompanied by sensory or motor

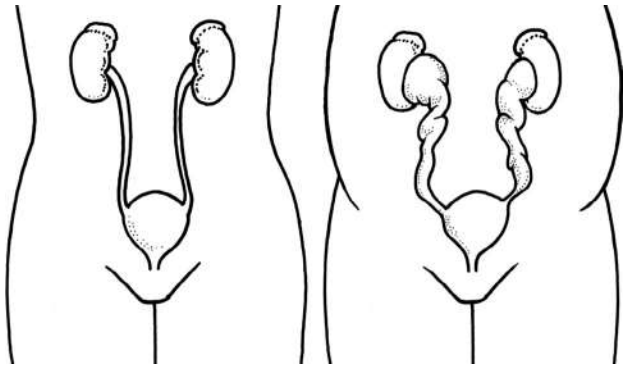


• **Figure 45.3** A group of 855 women studied between 12 menstrual weeks of pregnancy and delivery reported three types of pain. Back pain was reported by 49% of the women at some point during pregnancy. **A,** High back pain (10%). **B,** Low back pain (40%). **C,** Sacroiliac pain (50%). (Adapted with permission from Ostgaard HC, Andersson GBJ, Karlsson K. Prevalence of back pain in pregnancy. *Spine.* 1991;16:549–552.)

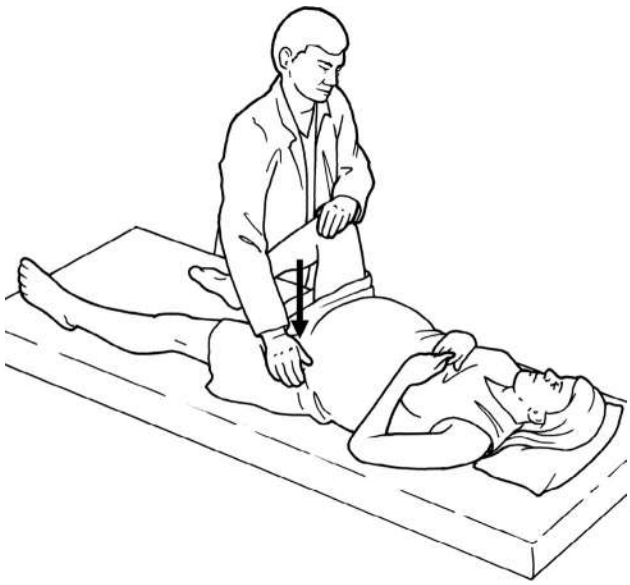
symptoms. When the clinical presentation is confusing, EMG can aid in differentiating peripheral nerve lesions, polyneuropathies, and plexopathies from single radiculopathies. However, false-negative EMG results are common, especially in the case of a HNP causing compression of a single nerve root.[143]

Prevention and Treatment of Back and Pelvic Girdle Pain

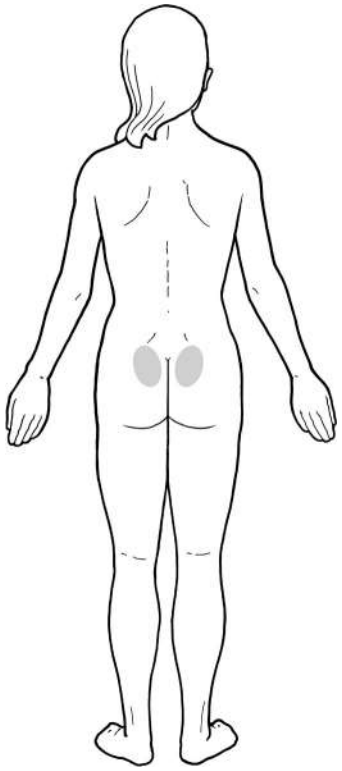
Few of the commonly used strategies to prevent low back pain during pregnancy are universally effective. Patients who were instructed in basic lifting techniques experienced significantly less backache than a control group who did not receive similar instruction.[144] Aerobic exercise can be prescribed safely throughout pregnancy.[144] However, maintenance of good physical conditioning may not alter the incidence of back pain during pregnancy.[145] Nonetheless, the American College of Obstetricians



• **Figure 45.4** Elevated progesterone levels and pressure from the expanding uterus lead to dilation of the ureters in pregnancy. Stasis in the urinary tract can lead to pyelonephritis. (Adapted with permission from Chamberlain G. ABC of antenatal care. Abdominal pain in pregnancy. *Br Med J.* 1991;302:1390–1394.)



• **Figure 45.5** The posterior pelvic provocation test. (Adapted with permission from Ostgaard HC, Zetherstrom G, Roos-Hanson E, et al. Reduction of back and posterior pelvic pain in pregnancy. *Spine.* 1994;19:894–900.)



• **Figure 45.6** Areas where pain is felt when the posterior provocation test is performed in women with posterior pelvic pain. (Adapted with permission from Ostgaard HC, Zetherström G, Roos-Hanson E, et al. Reduction of back and posterior pelvic pain in pregnancy. *Spine.* 1994;19:894–900.)

and Gynecologists recommends specific muscular conditioning exercises to promote good posture and prevent low back pain during pregnancy.[146]

Treatment of pregnancy related low back and PGP begins with the education of the common causes of pain during pregnancy. Back care classes are available that focus on anatomy, ergonomics, correct posture, and relaxation techniques. If the pain remains poorly controlled, referral to a physical therapist for instruction in body mechanics and low back exercises may be beneficial. In a recent Cochrane review of the treatment of low back pain, pregnant-specific exercise programs, physiotherapy, and acupuncture added to the usual prenatal care appeared to reduce back pain more than just usual prenatal care. Moreover, acupuncture may be more effective than physiotherapy. Participation in water gymnastics programs also reduced the number of back pain related work absences.[147]

Although the incidence of HNP during pregnancy is low, radicular symptoms are common and often accompany sacroiliac subluxation and myofascial pain syndromes. The use of epidural steroids outside of pregnancy remains controversial.[148] The strongest evidence for the efficacy of epidural steroids appears to be in patients with symptoms attributable to acute disk pathology.[149] Whereas the risk to the fetus following a single dose of an epidural corticosteroid appears to be low, it is our opinion that epidural steroids should be reserved for the parturient with the new onset of signs (e.g. unilateral loss of deep tendon reflex, sensorimotor change in a dermatomal distribution) and symptoms consistent with lumbar nerve root compression. We believe that it is reasonable to proceed with epidural steroid placement prior to obtaining imaging studies in such patients. Resolution of the radicular symptoms after epidural steroid treatment may well obviate the need for imaging studies.

Guided local anesthetic injection into the sacroiliac joint or the pubic symphysis can have diagnostic and therapeutic value.

TABLE 45.3 Sacroiliac Subluxation: Criteria for Diagnosis and Common Confirmatory Signs

Criterion or Sign	Description
Diagnostic Criterion	
Sacral pain	The pain is usually unilateral and, in some cases, radiates to the buttock, lower abdomen, anterior medial thigh, groin, or posterior thigh.
Positive Piedallu's sign	Forward flexion of the lower back results in asymmetric movement of the posterior superior iliac spines (PSISs), with one PSIS becoming higher than the other.
Positive pelvic compression	Pain in the sacral area is provoked by direct bilateral downward pressure on the anterior superior iliac spines (ASISs).
Asymmetry of the ASIS	The ASISs should be examined with the patient in the supine position to eliminate the effect of leg length discrepancy; in sacroiliac subluxation, one ASIS will be higher than the other.
Confirmatory Sign	
Straight leg raise	Passive raising of the patient's leg, with the knee extended and the patient in the supine position, causes pain, usually at the end range.
Flexion block	With the patient in the supine position, the knee is flexed at 90 degrees and then passively pressed toward the chest; flexion is blocked to half the expected range on the painful side.
Positive Patrick's test	Placing one heel on the opposite knee, in the recumbent position, and simultaneously rotating the leg outward provokes pain.
Pain at Baer's point	A point of acute tenderness is found just to the side and below the umbilicus on the painful side, which is about one-third of the way between the umbilicus and ASIS.

Adapted with permission from Daly JM, Frame PS, Rapoza PA. Sacroiliac subluxation: a common, treatable cause of low back pain in pregnancy. *Fam Pract Res J.* 1991;11:149–159.

• Box 45.3 Recommendations for the Use of Neurodiagnostic Imaging in the Pregnant Patient

- Determine the necessity of a radiologic examination and the risks involved.
- If possible, perform the examination only during the first 10 postmenses days. If the patient is pregnant, delay the examination until the third trimester, or preferably postpartum.
- Determine the most efficacious use of radiation for the problem.
- Use magnetic resonance imaging (MRI) if possible.
- Avoid direct exposure to the abdomen and pelvis.
- Avoid contrast agents.
- Do not avoid radiologic testing purely for the sake of pregnancy. Remember, you are responsible for providing the best possible care for the patient. The risk to the pregnant patient of not having an indicated radiologic examination is also an indirect risk to the fetus.
- If significant exposure is incurred by a pregnant patient, have a radiation biologist (usually stationed in the radiology department) review the radiology examination history carefully so that an accurate dose estimate can be ascertained.
- The decision to terminate pregnancy because of excessive radiation exposure is an extremely complex issue. Because any increased risk of malformations is considered negligible unless radiation doses exceed 0.1–0.15 Gy (10–15 rad). The amount of exposure that an embryo or fetus would likely receive from diagnostic procedures is well below the level for which a therapeutic abortion should be considered.
- Consent forms are neither required nor recommended. The patient should be informed verbally that any radiologic examinations ordered during pregnancy are considered necessary for her medical care. She should also be informed that the risks to the fetus from computed tomography or plain film radiography are very low and that there are no known risks to humans of MRI. Having the patient sign a consent increases the perceived risks and adds needlessly to her concerns during and after the examination.

Adapted with permission from Schwartz RB. Neurodiagnostic imaging of the pregnant patient. In: O Devinsky, E Feldmann, B Mainline (eds). *Neurologic Complications of Pregnancy*. New York, Raven Press; 1994: 243–248.

• Figure 45.7 Proper placement of a trochanteric belt to stabilize painful pelvic joints and decrease back pain.

As mentioned previously, most clinicians wish to limit exposure to ionizing radiation during pregnancy. Surface ultrasound can be used to aid in entry into the sacroiliac joint. Relief after an intra-articular injection is indicative only of intra-articular pathology. Extra-articular pathologies contributing to PGP, such as strain of superficial long sacroiliac joint ligament, are unlikely to improve after intra-articular injection.

Treatment options during pregnancy are limited by the presence of and potential hazard to the fetus. After delivery, the majority of women have improvement of their symptoms within a few months. Non-pharmacologic treatment modalities used during pregnancy include physical therapy with pelvic tilt exercises, use of support belts (Fig. 45.7), rotational manipulation of the sacroiliac joint, water gymnastics, transcutaneous electrical nerve stimulation (TENS), and acupuncture.[147] With the use of the TENS unit during pregnancy, there is a theoretical concern about inadvertent induction of labor through the use of certain acupuncture points and fetal cardiac conduction disturbances with the passage of current through the fetal heart. Limited data suggest that TENS is safe during pregnancy. A recent Cochrane review on the use of TENS for the treatment of pain during labor found no deleterious effects on the mother or the fetus.[150] Given the theoretical concerns, one recommendation for TENS use during pregnancy is to keep the current density low and avoid certain acupuncture points.[151]

Migraine Headache During Pregnancy

Causative Factors and Clinical Presentation

The clinician is often confronted with the occurrence of headaches during pregnancy as recurring headaches happen most commonly during the childbearing years. Migraine can be a disabling disorder that is more prevalent among women than men, thought in part because of the influence of female sex hormones.[152] Migraine headaches vary with female reproductive events, including menarche, menstruation, oral contraceptives, pregnancy, and menopause.[153] Eighty percent of female migraineurs report the onset of migraine at 10–39 years, suggesting that sex hormones play a significant role in the pathogenesis.[154] They typically improve in the first trimester of pregnancy when there is a sudden and sustained increase in estradiol levels.[155] In fact, 50%–80% of patients who suffer from migraines experience a significant reduction in frequency or total cessation of migraine attacks during pregnancy. However, women with headaches persisting into the second trimester are less likely to improve after that.

Migraine headaches rarely begin during pregnancy, but if they do, they typically occur during the first trimester. Many clinicians believe that the initial presentation of headaches during pregnancy should initiate a thorough search for potentially serious causes.[91,156] One report of nine women presenting with migraine-like headaches during pregnancy found that four were severely thrombocytopenic, two met the criteria for preeclampsia,

and one had a threatened abortion.[156] The literature is replete with reports of intracranial pathology that mimicked migraines during pregnancy, including strokes, pseudotumor cerebri, tumors, aneurysms, arteriovenous malformations, and cerebral venous thrombosis.[91] Metabolic causes of headache during pregnancy include illicit drug use (most notably, cocaine[157]), anti-phospholipid antibody syndrome, and choriocarcinoma.[158]

Evaluation

Patients who present with their first severe headache during pregnancy should be aggressively evaluated. Only when secondary causes of headache in pregnancy, including head trauma, cerebral venous thrombosis, preeclampsia, ICH or subarachnoid hemorrhage, ischemic stroke, vasculitis, or dehydration, have been ruled out should pregnant women be diagnosed with a primary headache. The first step is a detailed history and neurologic examination. Focal neurologic abnormalities, papilledema, and seizures in the setting of headaches warrant further investigation. Suggested diagnostic tests for new onset headache during pregnancy include urinalysis, blood chemistries, hematologic studies, liver function tests, and coagulation studies.[154] Brain imaging is also an important component of the workup. MRI without gadolinium is safe in all trimesters and should be the modality of choice during pregnancy.[154] In the patient who presents with sudden onset of the "worst headache of my life," a subarachnoid hemorrhage should be ruled out.[91] If the brain computed tomography (CT) is negative for hemorrhage, a lumbar puncture should be performed, and the spinal fluid should be evaluated for subarachnoid blood. Progressively worsening headaches in the setting of sudden weight gain should suggest preeclampsia or pseudotumor cerebri. The triad of elevated blood pressure, proteinuria, and peripheral edema point toward preeclampsia. Furthermore, hyperreflexia and elevated serum uric acid are also found in patients with preeclampsia.

Treatment and Prevention

For pregnant women with a history of migraines prior to pregnancy and a normal neurologic examination, the therapeutic challenge is to achieve control of the headaches while minimizing the risk to the fetus. Non-pharmacologic techniques, including relaxation, biofeedback, and elimination of certain foods, often suffice for treatment. Marcus and colleagues[159] have demonstrated a significant reduction in headache that continued throughout pregnancy and at the one-year follow up using a combination of relaxation training, thermal biofeedback, and physical therapy exercises.

If pharmacologic therapy appears warranted, acetaminophen with or without caffeine is safe and effective.[160] A drawback to acetaminophen is the potential for medication overuse and rebound headache, which could lead to the development of daily chronic headaches. Ibuprofen and naproxen are the most commonly used NSAIDs for abortive management of migraines. However, as discussed in the prior section, they can have significant effects on pregnancy. The short-term use of mild opioid analgesics such as hydrocodone, alone or in combination with acetaminophen, also appears to carry little risk (Table 45.1). When oral analgesics prove ineffective, hospital admission and administration of parenteral opioids may be required (Table 45.2).

Until more information is available on the safety of sumatriptan during pregnancy, it should be used only after other strategies have failed. Triptans are the most used abortive agent in nonpregnant patients but are rarely used during pregnancy. There are pregnancy registries for both sumatriptan and naratriptan to track pregnancy outcomes after exposure to these medications. At this time, there does not seem to be an increased incidence of teratogenicity or adverse pregnancy outcomes with use in the first trimester. Ergot preparations should be avoided during pregnancy and lactation. They are known to cause prolonged and marked uterine tone and impaired placental flow leading to fetal distress or spontaneous abortion.

A history of three to four incapacitating headaches per month warrants consideration of prophylactic therapy.[160] If the frequency of the headache is less than three to four per month, but they are severe and unmanageable with acute therapies, prophylactic therapy should be considered to prevent dehydration to the mother, which could cause fetal distress. Daily oral propranolol or atenolol are reasonable choices, although patients should understand that their use is associated with small for gestational age infants. Longer acting agents should lead to less fluctuation in maternal and fetal blood concentrations and perhaps less fluctuation in the drug effects on fetal heart rate. We prefer to use long-acting agents (e.g. atenolol or sustained-release propranolol) based on this theoretical advantage.

Although anti-depressants are effective for prophylactic therapy in nonpregnant patients, the most commonly used medications of this class (imipramine, amitriptyline, and nortriptyline) are typically avoided because of insufficient information in the pregnant patient. The selective serotonin receptor inhibitors can be used with caution, especially if there is comorbid depression. Limited anecdotal experience with calcium channel blockers (verapamil, nifedipine, and diltiazem) and mini dose aspirin (81 mg/day) suggests that they may be effective prophylactic agents during pregnancy.[91,160]

Migraine and Lactation

Postpartum headache is common and can occur in 30%–40% of all women.[153] Most occur in the first week, and about 50% of those who experience relief of their migraine during pregnancy have recurrence a short time after delivery. This phenomenon may be secondary to the rapid ovarian withdrawal of progesterone and estradiol. Lactation can inhibit ovulatory cycles during the puerperium and is characterized by increased prolactin levels and low estradiol levels. In bottle-feeding women, the hormonal cycle is rapidly restored, which may contribute to it being the main risk factor for postnatal recurrence of migraine.[162]

Pain in the Pregnant Patient With Sickle Cell Disease

Causative Factors and Clinical Presentation

Sickle cell disease is an inherited multisystem disorder. The presence of abnormal hemoglobin in red blood cells leads to the cardinal features of the disease, chronic hemolytic anemia, and recurrent painful episodes. Vaso-occlusive crisis is the most common maternal complication noted in parturients with sickle cell hemoglobinopathies.[161] Vaso-occlusive crises follow a characteristic pattern of sudden, recurrent pain attacks, usually involving the abdomen, chest, vertebrae, and extremities. One prospective study has demonstrated that the clinical course of women with sickle cell disease is not adversely affected by their pregnancy, as measured by the rate of painful episodes over 100 days.[163] The rate was constant before, during, and after the first pregnancy and subsequent pregnancies. Painful episodes occurred at some time during the course of 50% of pregnancies.

Most crises during pregnancy are vaso-occlusive and are often precipitated by urinary tract infection, preeclampsia or eclampsia, thrombophlebitis, or pneumonia. Clinically, the individual will describe pain in the bones or joints but may also perceive the soft tissues as being affected. Visceral pain is also common and may be related to events in the liver or spleen. Painful episodes can be variable in severity and duration, with most episodes lasting from three to five days.[164]

Evaluation

Because laboratory evaluation is nonspecific, diagnosis of vaso-occlusive crisis begins with excluding other causes for the painful episode, particularly occult infection.[162] Complete assessment and the acute management of sickle cell crisis in pregnancy has been reviewed by Martin and coworkers.[165]

Treatment

Management of vaso-occlusive crisis during pregnancy is primarily supportive and symptomatic. A 2009 Cochrane review of intervention for treating a sickle cell crisis during pregnancy attempted to assess the effectiveness and safety of commonly used treatment regimens including red cell transfusion, oxygen therapy, intravenous hydration, analgesic drugs, and steroids. There are no randomized clinical trials on this topic, in part because pregnant women tend to be excluded from clinical trials.[166] Most clinicians begin management with aggressive hydration to increase intravascular volume and decrease blood viscosity.[165] Supplemental oxygen is essential in those patients with hypoxemia. Partial exchange transfusions to reduce polymerized hemoglobin S remain an integral part of the management of sickle cell disease.[167] Prophylactic transfusions may reduce the incidence of severe sickling complications during pregnancy.[168]

Education about how pregnancy interacts with sickle cell disease can help reduce depression or anxiety, often decreasing the pain that the patient is experiencing. Biofeedback has been shown to reduce the pain of sickle cell crises and the number of days that analgesics were taken.[169] Physical therapy techniques (e.g. exercise, splinting, local application of heat) can also be helpful.[170] TENS may be helpful when pain is isolated to a limited region.[171]

The severity of pain dictates the pharmacologic approach to managing sickle cell pain. Although non-opioid analgesics may suffice, oral or parenteral opioids are often required (Tables 45.1 and 45.2). Acetaminophen remains the non-opioid analgesic of choice during pregnancy. Although NSAIDs can be useful adjuncts, particularly for controlling bone pain, they should be used cautiously during pregnancy. Oral analgesic combinations containing acetaminophen and hydrocodone or another weak to moderate potency opioid can be added for more severe pain.

For the hospitalized patient with severe sickle cell pain, potent opioid analgesics administered intravenously may be necessary to control pain adequately (Table 45.2). Morphine sulfate is well tolerated and effective for control of severe sickle cell pain.[172] Fentanyl and hydromorphone provide reasonable alternatives for patients who cannot tolerate morphine. Administration of morphine via PCA device allows patients a sense of control over their illness. Weisman and Schecter[173] have noted that significantly higher doses of opioids may be necessary for the control of vaso-occlusive crisis pain than postoperative pain. In our practice, we aggressively treat individuals with severe sickle cell pain with potent opioids administered via PCA (most often using morphine). As the pain of vaso-occlusive crisis begins to resolve, patients are transitioned to a long-acting oral opioid (such as sustained-release morphine). This approach allows earlier ambulation and hospital discharge. All opioids are then tapered over the following 7–10 days.

The use of regional anesthesia has not been formally studied in sickle cell disease. There are case reports describing epidural analgesia to treat a sickle cell crisis during pregnancy in parturients with pain localized to the trunk or lower extremities.[174,175] This technique offers the theoretical advantage of increased microvascular blood flow while providing pain relief without opioids.

Acute Pain in Opioid Dependent Patients

Acute pain in the pregnant patient is most often encountered during labor and delivery. Both pain control and withdrawal symptoms are mediated through the μ-opioid receptor. Therefore opioid pain medication requires the availability of the μ-opioid receptor, which in opioid dependent patients is also occupied by opioid agonist therapy for dependence. No randomized or controlled studies are available to determine whether anesthetic needs differ in opioid dependent patients compared to control patients. One descriptive study has found that 24% of opioid dependent women had difficulty with labor analgesia, and 74% had difficulty with post-Cesarean analgesia.[176] These statistics may overestimate the difficulty in pain control because it was not clear that treatment of opioid dependence was adequate prior to treatment for acute pain. When opioid dependence is untreated and combined with acute pain, opioid needs reflect the combined therapies rather than treatment for pain alone. Although no randomized clinical trials have been performed, we have found that epidural analgesia with a standard dose of local anesthetic and low dose opioid (e.g. 0.0625% bupivacaine with fentanyl, 2 mg/mL) provides adequate intrapartum analgesia.

Intrathecal or epidural analgesia using only opioids may not be effective in reducing the need for systemic opioids. Sustained administration of m-opioid agonists by any route can induce both opioid tolerance and abnormal pain similar to neuropathic pain.[177] Although previously attributed to pharmacologic tolerance, patients maintained on methadone may experience opioid-induced hyperalgesia, a paradoxical effect mediated in part by the neurotransmitter *N*-methyl-D-aspartate and possibly by the novel neuropeptide dynorphin.[178] Interestingly, dynorphin may be an important mediator of chronic neuropathic pain, a common complaint among opioid dependent patients.

There are no trials that investigate opioid use and pain control after vaginal or abdominal delivery in opioid-tolerant patients. Recently published guidelines for the treatment of acute pain in patients maintained on methadone or buprenorphine provide a reasonable approach until more data are available.[54] Patients maintained on methadone for opioid dependence should have their methadone continued at the same dose in addition to standard dose opiates as needed for acute pain. The use of non-opioid analgesics should be included, but additional opioid medication should not be withheld. This additional short-acting opioid medication can be gradually discontinued as clinically indicated. If patients cannot tolerate oral medication, methadone can be administered intramuscularly or subcutaneously in two to four divided doses.

Patients maintained on buprenorphine pose a more difficult dilemma in the postoperative period. As a combined opioid agonist-antagonist, continued administration of buprenorphine can block the μ-mediated analgesic effect of additional short-acting opioids.[179] It is of note that although nonpregnant patients receive a combination of buprenorphine and naloxone, monotherapy is prescribed during pregnancy with buprenorphine to avoid naloxone exposure by the neonate.[180] Pain control options

and non-opioid analgesics include the following[54]: adding short-acting opioids with the realization that larger doses may be needed or dividing the daily dose of buprenorphine into 6 hour intervals, which can take advantage of the short-term analgesic effect of buprenorphine. Suppose buprenorphine is going to be discontinued with the initiation of another opioid, such as methadone. In that case, this approach is best attempted with the help of an addiction specialist because restarting the buprenorphine after the acute pain has been resolved can precipitate withdrawal if not carefully managed. In general, buprenorphine should be restarted only when patients have mild withdrawal symptoms (not before) to prevent antagonistic effects at the μ-opioid receptor.

Conclusion

Many physicians find themselves apprehensive about treating pain in pregnant patients. Evaluation and treatment are limited by the relative contraindication of radiography in the workup and the risks associated with pharmacologic therapy during pregnancy. Nonetheless, familiarity with common pain problems and the maternal and fetal risks of pain medications can allow the pain physician to help women achieve a more comfortable pregnancy. A single healthcare provider should be designated to coordinate specialist evaluations and integrate their suggestions into a single integrated care plan.

Key Points

- Medical management of the pregnant patient should begin with attempts to minimize the use of all medications and use non-pharmacologic therapies whenever possible.
- The most critical period for minimizing maternal drug exposure is during early development, from conception through the tenth menstrual week of pregnancy.
- Most breast milk is synthesized and excreted during and immediately following breastfeeding. Taking medications after breastfeeding or when the infant has the longest interval between feedings and avoidance of long-acting medications will minimize drug transfer via breast milk.
- There is no role for routine use of NSAIDs for pain other than that related to rheumatologic disease or uterine fibroids.
- All NSAID use for pain should be discontinued by 34 weeks gestation to prevent pulmonary hypertension in the newborn.
- All opioid analgesics carry teratogenic risk but can be used to monitor acute and chronic pain.
- For the opioid dependent parturient, buprenorphine has been found to be superior to methadone in reducing signs of withdrawal in newborns, thus requiring less medication and hospitalization time for the babies.
- Benzodiazepines should be avoided during organogenesis, near the time of delivery, and during lactation.
- Fifty percent of women will experience low back pain during their pregnancy, and it is commonly looked upon as a normal part of pregnancy.
- Although the incidence of HNP during pregnancy is low, radicular symptoms are common and often accompany sacroiliac subluxation and myofascial pain syndromes.
- Migraine headaches rarely begin during pregnancy, but if they do, they typically occur during the first trimester.
- Patients who present with their first severe headache during pregnancy should be aggressively evaluated, and only when secondary causes of headache in pregnancy have been ruled out should pregnant women be diagnosed with a primary headache.
- Postpartum headache is common and can occur in 30%–40% of all women. Most occur in the first week, and about 50% of those who experience relief of their migraine during pregnancy have recurrence a short time after delivery.
- Vaso-occlusive crisis is the most common maternal complication noted in the parturient with sickle cell hemoglobinopathies.
- Evaluation and treatment of the parturient with pain are limited by the relative contraindication of radiography in the workup and the risks associated with pharmacologic therapy during pregnancy.

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Rheumatologic Conditions

DAVID ANDREW WALSH

Introduction

Rheumatology is the study of rheumatism, arthritis, and other disorders of the joints, muscles, and ligaments.[1,2] Rheumatologic conditions are highly prevalent. Nearly one-fifth of the United Kingdom population reports a chronic musculoskeletal system condition. Rheumatologic conditions commonly begin during working life, with the peak incidence of gout and rheumatoid arthritis in late working life, although many people are afflicted by inflammatory arthritis in early adulthood or even childhood. Rheumatologic conditions are complex and heterogeneous and require multi-disciplinary approaches to their management. Health systems across the world structure rheumatologic care in different ways, often involving physicians with rheumatologic and general medical expertise, orthopedic surgeons, experts in metabolic bone disease, nurses, physiotherapists, occupational therapists, orthotists, podiatrists, and others. The patient should always be at the center of the team. Pain is the main, although not the only, problem described by people with rheumatologic conditions. Rheumatologic pain management depends on principles and research from other disciplines, incorporating both pharmacologic and non-pharmacologic approaches. Specific aspects of the function of the musculoskeletal system and the nature of rheumatologic conditions may require disease-specific approaches to pain management. Pain and function are closely integrated, and physiotherapy and occupational therapy aim to address both concurrently. Common chronic conditions such as osteoarthritis, rheumatoid arthritis, and gout illustrate persistent chronic and episodic acute pain associated with musculoskeletal disease.

Osteoarthritis is the most common form of arthritis, and its prevalence increases with age. Osteoarthritis subgroups may be defined based on the joint distribution (e.g. knees, hips, or small joints of the hands) or precipitating factors (e.g. primary, post-traumatic, or secondary to inflammatory arthritis). Osteoarthritis affecting major weight-bearing joints substantially impacts mobility and function, although small joint osteoarthritis in the hands or feet can also cause substantial distress and disability.

Rheumatoid arthritis is the most common form of inflammatory arthritis, affecting approximately 1%-2% of the Western population. People with inflammatory arthritis report pain as their highest priority for improvement.[3,4] Inflammatory arthritis is an autoimmune condition characterized by immune-mediated inflammation of the joint lining (synovitis) and, if inadequately controlled, consequent joint damage and secondary osteoarthritis. Seronegative inflammatory arthritis may be associated with psoriasis, colitis, ankylosing spondylitis, or reactive arthritis that may follow infection, and each has its own specific genetic and immunologic characteristics. Rheumatoid arthritis has a predilection for small joints of the hands and feet and often affects the knees, shoulders, ankles, or wrists in a symmetrical polyarticular distribution. Seronegative spondyloarthropathies often affect small numbers of weight-bearing joints (oligoarthritis) and/or the axial skeleton, although polyarticular distributions are not uncommon. Seronegative spondyloarthropathies are characterized by enthesopathy (inflammation at ligament insertions) and tendon sheath inflammation. Therefore inflammatory pain might not always be associated with localized joint swelling, and "tender points" because of inflammation might overlap with those associated with fibromyalgia. Pain and stiffness in inflammatory arthritis vary during the day, with the most pronounced symptoms usually in the morning, explained in part by diurnal variation in endogenous glucocorticoids. Disease onset may be acute or insidious, and early disease may be difficult to diagnose. Classifying these conditions as "inflammatory" does not deny the important contributions of inflammation to joint pain in osteoarthritis and gout.

Crystal diseases are characterized by acute, severe episodes of pain caused by the innate inflammatory responses triggered by crystal deposits. High circulating uric acid concentrations because of inadequate renal clearance or increased production (e.g. during chemotherapy) may favor urate crystal deposition and attacks of gout. In calcium pyrophosphate deposition (CPPD), crystals may trigger attacks that are indistinguishable from gout and are therefore called pseudogout. Calcium pyrophosphate deposition in articular cartilage may be detected radiologically as chondrocalcinosis, even in the absence of acute attacks. In CPPD, crystal formation may be associated with various metabolic disorders involving divalent cations (e.g. Wilson's disease). Gout and pseudogout may be associated with OA. Attacks typically affect a single joint, such as the knee, or, particularly in gout, first metatarsophalangeal, or interphalangeal joint. However, any synovial joint may be affected, and oligoarthritis or even polyarticular acute presentations may occur.

Non-inflammatory genetic connective tissue disorders associated with hypermobility are commonly associated with chronic musculoskeletal pain. Hypermobility syndromes include Marfan syndrome, Ehlers-Danlos syndrome, and Stickler syndrome, associated with genetic variation in fibrillin-1, collagen Col3/Col5, or Col2/9/11, respectively.[5] However, most people with joint hypermobility (perhaps 10% of the population) have a medically benign condition on a polygenetic background.

The Experience of Rheumatologic Pain

Pain is rarely a single experience, and people with rheumatologic conditions may report multiple qualities of pain. Rheumatologic pain may be described using any of the terms embedded within the McGill pain questionnaire, both those commonly associated with nociceptive and those characteristic of neuropathic pain.[6] The characteristics of osteoarthritis, inflammatory arthritis, and crystal disease often overlap, and these conditions may be comorbid. Evidence and experience from one rheumatologic condition may sometimes be generalizable to others, although caution should be exercised when such generalizations are not based on sound evidence.

In osteoarthritis, pain may occur only on weight-bearing or during joint movement or may be persistent at rest. Intermittent pain may be short-lived but severe, interspersed with periods that are pain-free or with less intense but constant pain.[7] Acute flares may be spontaneous and unexplained or may be attributed to unaccustomed activity. Periods of exacerbation might last weeks or months, and the unpredictability of intermittent pain can prevent forward planning. Pain may be progressive or may subside or resolve.

In rheumatoid arthritis, pain is often associated with joint inflammation, as evidenced by soft tissue swelling, synovial effusion, increased local temperature, and tenderness. Each of these features typically varies over time, either spontaneously or with treatment. However, such variations in inflammation and pain are not always concurrent. An increase in pain may herald an imminent inflammatory flare, and reductions in acute phase reactants on blood tests may precede symptomatic improvement.

Episodic and severe pain characterizes crystal arthropathies, such as gout or pseudogout. During an attack, the affected joint becomes red, hot, and swollen and is exquisitely tender to the extent that movement or weight-bearing might be impossible, and the weight of bed clothes can be intolerable. These signs resemble acute infection, which is an important differential diagnosis that must be excluded. However, between attacks, the joint is typically pain-free.

Pain is not the only symptom of rheumatologic disease, and people differ in how they understand or separate their pain from comorbid symptoms. Pain exists alongside fatigue, stiffness, and disability. Sleep disturbance and depressive symptoms are more common in people with inflammatory arthritis than in the general population.[8] Joint stiffness is particularly a feature of inflammatory joint diseases such as rheumatoid arthritis when it characteristically varies during the day and increases with increased inflammatory disease activity. Morning stiffness lasting more than an hour is not unusual during active synovitis, even though it may ease joint movement and activity. People with osteoarthritis also describe stiffness, which may reflect the inflammatory components of their disease. The reduced movement might also be because of structural changes, such as loss of articular cartilage, bony outgrowths at joint margins (osteophytes), or joint capsule fibrosis and tendon contracture. This type of stiffness, unlike stiffness associated with inflammation, displays slight diurnal variation.

Stiffness is a symptom rather than a sign, and the feeling that a joint does not move freely results from multiple mechanisms in and around the joint and in the central nervous system. Central mechanisms contribute to stiffness. People with rheumatoid arthritis who have undergone limb amputation may describe phantom stiffness, which varies during the day, and with generalized inflammatory flares of their arthritis.[9] People often find it difficult to disentangle their experiences of pain and stiffness. Indeed "stiffness," which is unpleasant and associated with tissue damage, would satisfy the International Association for the Study of Pain (IASP) definition of pain[10] and might therefore be considered a component of the pain experience.

Fatigue is a common accompaniment of rheumatologic pain and has been reported as the second most troublesome symptom in people with rheumatoid arthritis. People may attribute their fatigue to sleep disturbance, for example, being woken by joint pain when turning during the night. However, sleep disturbance, unpleasant in its own right, is not an inevitable cause of fatigue, and additional biopsychosocial factors are important. Sleep disturbance and fatigue may be associated with evidence of central sensitization in osteoarthritis or rheumatoid arthritis,[11] as it is also associated with widespread chronic pain. Circulating cytokines may contribute to fatigue in people with systemic inflammation.[12] Fatigue is associated with a low mood, even in the absence of chronic musculoskeletal pain. Regardless of its underlying mechanisms, fatigue is associated with chronic musculoskeletal pain, is an important symptom in its own right, and can be a barrier to effective pain management. Overwhelming fatigue challenges the individual's ability to cope with their pain and limits their ability to exercise as a form of therapy.

Difficulties with acceptance, psychological distress (anxiety and depression), catastrophizing, and cognitive impact are key components of rheumatologic pain, not less than in other chronic pain states. Patients may have difficulty accepting their rheumatologic condition, which in most cases will not be amenable to cure, but instead, require lifelong treatment with associated risks and inconvenience. When newly diagnosed, people often display psychological reactions comparable to grieving, reflecting their permanent loss of good health. Persistent pain may be interpreted (both by patient and clinician) to indicate persistent inflammation, treatment failure, and ongoing joint damage, even when inflammation has been completely suppressed. Fear that pain on activity inevitably indicates ongoing joint damage can be a barrier to rehabilitation and exacerbates declining function.

In addition to constituting the key emotional components of pain, psychological distress may be associated with central sensitization,[13] augmenting nociceptive signaling, and the sensory dimensions of pain. Pain's ability to distract attention and impair cognitive processing can compromise both work and leisure. With modern immunosuppressive therapy, people now developing rheumatoid arthritis might expect to live normal lives, engage in work, sports, and other activities alongside those without disease. However, the unpredictability of flares can prevent the planning of valued activities, including work and vacations, and undermine an individual's self-esteem. Self-efficacy and successful self-management require control over persistent and intermittent symptoms and suppression of the underlying pathology.

Suppressing pain in people with rheumatologic conditions is urgently needed. Furthermore, delays in effective pain management can lead to disability and loss of gainful employment, which may be difficult to reverse. Inadequate pain management in people with rheumatologic conditions is a risk factor for future pain, psychological distress, lost work productivity, healthcare utilization, and poor response to later definitive interventions such as joint replacement surgery.[6,14] Pain management aims to improve symptoms and modify a key risk for future adverse outcomes, both for the patient and society.

Why Are Rheumatologic Conditions Painful?

Mechanisms of rheumatologic pain include changes in the peripheral musculoskeletal system, sensitization of peripheral and central nociceptive pathways, changes in brain connectivity, experience, and interpretation within a psychosocial context. Each pain mechanism is modulated by constitutional risk factors and comorbidities. Mechanisms may be shared or may differ between diseases, between individuals, and across time within an individual. Different mechanisms underlie different aspects of the pain experience, including pain quality, periodicity, associated symptoms, impact, and response to treatment.

The musculoskeletal system is designed for weight-bearing and movement, and biomechanical factors contribute significantly to rheumatologic pain. Pain on normal movement might indicate sensitization within either the peripheral or central nervous system. Sensitization might result from actions on peripheral nerves by chemical mediators, including growth factors or cytokines. Structural changes may redistribute forces within the joint. Thinned, irregular, or inelastic articular cartilage may be unable to adequately dissipate force, thereby activating nerves that are normally present in the subchondral bone. Hypermobility, for example, may be associated with patellar maltracking and consequent anterior knee pain. Nociceptive transduction may be increased by abnormal interactions between sensory nerve terminals and adjacent connective tissue molecules.

Loss of osteochondral integrity can expose subchondral nerves to molecules generated by the synovium, which may further stimulate subchondral inflammation and neuronal sensitization. Normal forces may activate nerves that have grown into the articular cartilage or knee menisci during structural disease progression.[15,16] These joint structures were not innervated in the normal joints.

Peripheral sensitization is a key component of rheumatologic pain. Inflamed or damaged tissues generate cyclo-oxygenase products, bradykinin, and nerve growth factor (NGF). These may either activate or sensitize the peripheral terminals of the primary nociceptive afferents. Urate (gout) or calcium pyrophosphate dihydrate (pseudogout) crystals trigger leukocyte degranulation and an acute innate immune response. In chronic rheumatoid arthritis or osteoarthritis, NGF, cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)α, and chemokines may be upregulated in the synovium and subchondral bone.[17] NGF has been identified as a key cause of peripheral sensitization in osteoarthritis[18] and may also contribute to pain in rheumatoid arthritis.[19] NGF induces phosphorylation of transient receptor potential cation channel subfamily V member 1 (TRPV1). It increases the expression of substance P, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor in the dorsal root ganglion and increases the levels of transmitters and modulators at the first synapse within the dorsal horn. Systemic factors, such as circulating autoantibodies or immune complexes, might also interact with primary afferent nociceptors to increase sensitization in rheumatologic conditions.[20]

Persistent nociceptive barrage, the release of growth factors, and glial cell activation within the central nervous system, and changes in descending nociceptive control, contribute to central sensitization in rheumatologic conditions. With persistent joint pathology and nociceptive drive, central pain mechanisms become increasingly important. Functional connectivity may be enhanced between brain areas involved in sensory and emotional experiences, aggravating the emotional component of pain.[21]

Pain experience depends on psychosocial context. An increased understanding of the underlying mechanisms of rheumatologic disease has led to major advances in immunologic treatments in recent decades. However, pain and inflammation can be discordant.[22] A patient who is informed that their inflammatory disease is well controlled may feel that their pain experience is invalidated or not believed. Pain does not even need to be present in order to be a problem, for example, if a patient fears future severe or unpredictable flares.

Different individuals experience pain differently, despite apparently similar rheumatologic pathologies. Such diversity depends, in part, on genetic heterogeneity. Genotyping studies in painful osteoarthritis have identified polymorphisms in genes that are anticipated to influence joint shape and structure, but also in genes that regulate neuronal function or analgesic responses. Sex differences in rheumatologic pain similarly reflect both the propensity for joint pathology and differences in nociceptive processing.[23]

Assessment of Painful Rheumatologic Conditions

Pain is the dominant symptom in most rheumatologic conditions, and patient-centered assessment should include evaluation of the nature, severity, and consequences of pain. Assessment should also address pain mechanisms, such as using biomarkers linked to diagnosis or pathology, to demystify this most bothersome symptom and help select treatments most likely to be of benefit. Careful attention to multimorbidity can inform prognosis, maximize health benefits, and reduce risks from pain treatments. Understanding and informing patients' expectations and preferences facilitates treatment convergence

Rheumatologic Pain

Pain assessment aims to identify its nature, severity, and importance to the patient and is essential for evaluating treatment response. Where pain is the presenting problem, assessment is inevitably incomplete without a detailed pain assessment. Pain is a subjective experience, and only patients can provide the gold standard measurement.

Tools for evaluating pain may be generic or disease-specific. Assessment tools used in clinical practice often differ from those used in research because of the different requirements of validity, feasibility, and sensitivity to change. In the clinic, we are interested in the individual's pain, whereas research often seeks to understand the average effects across populations. Research might seek to explore mechanistic subgroups for whom there is currently no effective treatment, whereas clinical practice aims to identify problems for which interventions may be helpful. Pain is a subjective experience whose mechanisms are complex and are often unknown. Therefore assessment should embrace the patient's subjectivity rather than seek objective indices that might bear little relevance to the patient's problem.

In general, patient-centered pain outcome measures focus on the impact of pain on function (physical, psychological, sleep). Putative mechanistic tools, such as measuring neuropathic-like qualities, may inadequately address the problems of people with rheumatologic conditions.[24] Pain rarely occurs as a symptom in isolation, such that rheumatologic-specific outcome measures often include pain alongside other factors such as stiffness and fatigue.[25,26] Pain outcome measures might be incorporated into the more generic quality of life tools such as the medical outcomes study short form 36 (SF36) and EuroQol questionnaires. These

quality of life measures lack focus on individual joints but instead address the overall burden of commonly comorbid painful conditions. More specific outcome tools might be more able to detect responses to treatments that target a single joint or pain mechanism.

Osteoarthritis pain may be measured using self-report tools such as the intermittent and constant osteoarthritis pain (ICOAP) questionnaire,[7] pain subscales of the Western Ontario and McMaster Universities arthritis index (WOMAC),[27] or knee injury, and osteoarthritis outcome score (KOOS).[28] WOMAC contains five items related to weight-bearing or non-weight-bearing pain and has demonstrated a two factor structure through which weight-bearing and non-weight-bearing OA pain may be associated with different pathologic mechanisms. For example, weight-bearing pain was specifically associated with bone marrow lesions in weight-bearing joint compartments on MRI.[29] KOOS extends the WOMAC items to improve targeting for people with lower pain intensities or musculoskeletal injuries. The ICOAP was developed following qualitative assessment of pain in people with knee or hip OA and displayed a two factor structure corresponding to the intermittent or constant pain. People with early disease may experience predominantly intermittent pain, whereas those with advanced OA report intermittent on a background of constant pain, suggesting changes in pain mechanisms when the structural disease progresses.

The management of rheumatoid arthritis has traditionally focused on suppressing joint inflammation. Pain is assessed as one of the cardinal features of inflammation. However, pain in rheumatoid arthritis may also involve non-inflammatory mechanisms. The 28 joint disease activity score (DAS28) is a frequently used outcome measure in clinical trials of immunomodulatory treatments and clinical practice.[6] This composite tool incorporates tender joint counts (TJC) and swollen joint counts (SJC) based on a standardized set of 28 joints that are relatively frequent and specific for rheumatoid arthritis. TJC is classified by the application of standardized pressure (to blanch the assessor's nail bed) over each joint line. SJC is determined by the soft tissue swelling observed by a clinician. TJC and SJC are combined with a 100 mm visual analog scale of general health over the past week (VAS-GH) and a laboratory measure of an acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). VAS-GH is highly correlated with patient-reported pain. Therefore DAS28 comprises self-reported (VAS-GH and TJC) and observed (ESR/CRP and SJC) components. Synovitis may increase ratings for each component, whereas central sensitization may selectively increase VAS-GH and TJC. Therefore the difference between TJC and SJC has been proposed as an index of non-inflammatory pain mechanisms in rheumatoid arthritis.[30] High DAS28 is used in several countries as a criterion for commencing or continuing immunomodulatory treatments. The use of DAS28 in this way depends on a clear understanding of the contribution of pain to inflammatory disease assessment. Inappropriate escalation of immunomodulatory treatments in people whose pain is attributable to non-inflammatory mechanisms exposes them to risks with little likelihood of benefit.

Pain-Related Biomarkers

Biomarkers can help direct the treatment of rheumatologic conditions by indicating diagnosis and identifying and measuring peripheral or central pain mechanisms. Biomarkers may predict the prognosis or treatment outcomes. In general, those who have suffered worse pain in the past may have a worse pain prognosis, and those whose pain will persist or deteriorate stand to gain the most benefit from treatment. Treatments that target a particular mechanism might be expected to work best for those in whom this mechanism drives pain. Biomarker levels might change before patient-reported outcomes deteriorate or improve, opening opportunities for early intervention and accelerating the development of new treatments. Biomarkers may enable early discontinuation to minimize the risk of treatment in those destined to not respond and those who will suffer adverse events.

Diagnostic Biomarkers and Genetic Risk

Despite the overlap in pain mechanisms across diseases, the nature and responses to treatment of rheumatologic pain may vary between diagnoses. Biomarkers may be used to aid diagnosis. Specific connective tissue genetic variants directly cause hypermobility syndromes, such as Ehrlers' Danlos syndrome. Other genetic variants may predispose to rheumatologic conditions (for example, human leukocyte antigen B27 [HLA-B27] in spondyloarthropathies). Genetic variants encoding neuronal proteins, such as ion channels, may either predispose to or protect against rheumatologic pain. Other genetic variants, such as μ-opioid receptors, might influence the responsiveness to analgesic drugs.

Circulating autoantibodies to citrullinated peptides or double-stranded DNA have moderate to high specificity for rheumatoid arthritis and systemic lupus erythematosus, respectively. Radiographic features contribute to diagnostic classification, such as osteophytes for osteoarthritis, bony erosions at joints affected by inflammatory arthritis, and spinal syndesmophytes or sacroiliac joint fusion in ankylosing spondylitis. Hyperuricemia is a risk factor for gout and radiographic chondrocalcinosis for pseudogout, although the definitive diagnosis of these conditions requires the identification of crystals in joint fluid aspirates. Diagnostic biomarkers might be particularly important in early disease when the link between diagnosis and pain mechanism may be the strongest. Comorbid osteoarthritis or fibromyalgia may reflect increasing mechanistic complexity of pain with increasing time from disease onset.

Diagnostic classification may help predict pain prognosis and treatment response. Radiographic evidence of osteoarthritis predicts pain persistence and persistent pain severity in people with knee pain.[31] Diagnosis may also predict the response to treatment. However, diagnostic uncertainty may prevail, particularly in cases of early disease. The earliest stages of osteoarthritis might not be reliably classified by plain radiographs, and early rheumatoid arthritis may be mimicked by self-limiting parvovirus infection. Diagnostic uncertainty should not prevent adequate pain management.

Biomarkers of Peripheral Pain Mechanisms

Biomarkers that may point to pain mechanisms within the joint and are amenable to intervention include indices of inflammation and joint structural pathology.

Acute phase reactants such as ESR or CRP and ultrasound or MRI evidence of inflammation are useful indicators of peripheral drives to rheumatologic pain across multiple diagnoses, such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Raised acute phase in rheumatoid arthritis predicts worse structural outcomes, but not pain outcomes,[32] perhaps because modern treatments can effectively suppress the inflammatory components of the disease. Similarly, raised acute phase or MRI evidence of spinal inflammation in ankylosing spondylitis predicts better outcomes on biologic therapy.[33] However, precise

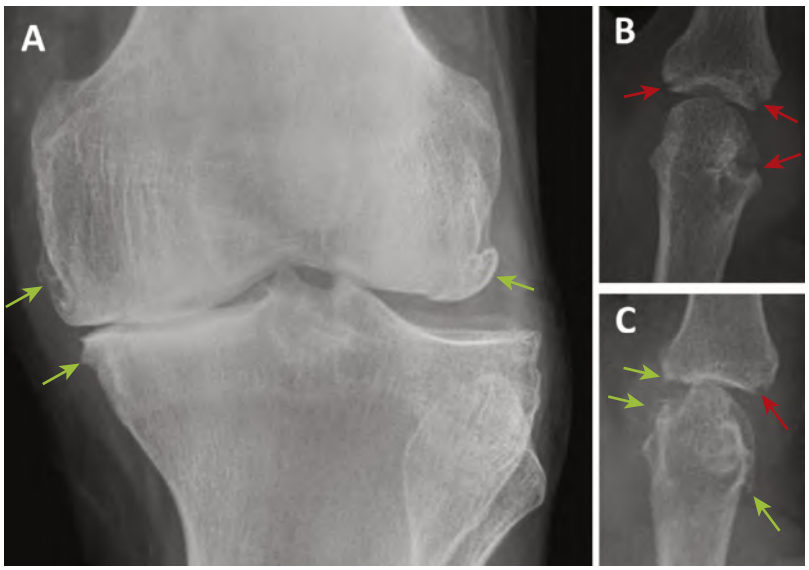
mechanisms of rheumatologic pain often remain ill-defined, and these "indices" should not be over-interpreted as direct causes of pain. For example, CRP production in the liver is dependent on IL-6, and IL-6 blocking antibodies reduce circulating CRP concentrations irrespective of their effect on pain. Shortly after the onset of polyarthritis, the high acute phase might paradoxically be associated with a good prognosis if, rather than rheumatoid arthritis, the patient has an acute synovitic response to viral infection.

Greater joint space narrowing on weight-bearing knee radiographs is associated with greater pain severity in cross-sectional studies and predicts worse pain outcomes in longitudinal community studies of osteoarthritis but better outcomes from joint replacement surgery (Fig. 46.1). However, the association between radiographic changes and pain in osteoarthritis is weak. Radiographic erosive joint damage or comorbid hand osteoarthritis at presentation with rheumatoid arthritis may be only weakly associated with pain and does not predict chronic pain with long term treatment,[34] consistent with a predominant drive to pain from non-structural mechanisms. MRI may provide more detailed biomarkers of the peripheral pain mechanisms. In osteoarthritis, subchondral bone marrow lesions and synovitis have consistently been associated with pain, both in cross-sectional and longitudinal studies.[35] Other MRI features, including knee meniscal extrusion or cartilage defects, may also be associated with pain, and close associations between different aspects of osteoarthritis structural pathology raise uncertainty about which features directly cause pain.

Biomarkers of Central Pain Mechanisms

Quantitative sensory testing (QST) evidence of sensitization is associated with higher concurrent pain severity in osteoarthritis,[36] and rheumatoid arthritis.[37] Mechanical stimulation modalities such as blunt or cuff-induced pressure or punctate stimulation of the skin may be more relevant to rheumatologic pain than thermal modalities, although it is uncertain whether sensitization mechanisms are specific to particular nociceptor subtypes. Baseline QST evidence of sensitization predicts worse pain at follow up and worse pain progression.[38] Much evidence has been derived from static mechanical QST modalities, such as pressure pain detection thresholds (PPT). PPT distal or remote from affected joints has been taken as an indication of central sensitization, whereas PPT at the joint may reflect a combination of peripheral and central sensitization.[39] Dynamic QST modalities such as temporal summation (TS) and conditioned pain modulation (CPM) more directly reflect central sensitization. Greater TS may indicate sensitization at the spinal cord, whereas lower CPM may indicate supraspinal deficiencies in endogenous analgesic mechanisms. Dynamic QST modalities may better predict pain outcomes in rheumatologic diseases than does PPT.[37,38] Evidence of central sensitization might predict worse pain outcomes in rheumatologic conditions by indicating resistance to treatments directed at the peripheral nociceptive drive.

Several phenotypic characteristics have been associated with QST evidence of central sensitization, leading to the proposal that self-report questionnaires might be used to indicate central sensitization in people with rheumatologic conditions.[13] In people with knee pain, psychological distress (depressive or anxiety symptoms), catastrophizing, sleep disturbance, fatigue, cognitive interference, neuropathic-like symptoms, and more widespread pain were each associated with lower PPT distal to the affected knee. These eight characteristics each contributed to a single factor, the central mechanisms trait, which was more strongly associated with PPT than was any one of the eight characteristics alone. Higher central mechanisms trait scores were associated with more severe pain and predicted worse pain outcomes in community dwellers with knee pain.[40] Similar self-report characteristics predict poor pain outcomes in other rheumatologic and non-rheumatologic conditions,[41] and contribute to the diagnostic classification of fibromyalgia.



• **Figure 46.1** Radiographic change in osteoarthritis and rheumatoid arthritis. (A) Posteroanterior radiograph of the knee of a person with structural changes of tibiofemoral osteoarthritis. The lateral joint compartment can be identified by the localization of the fibula. The medial tibiofemoral joint space is narrowed, with marginal osteophytes (*green arrows*) and subchondral sclerosis. (B and C) Plain radiographs of second metacarpophalangeal joints of two people with rheumatoid arthritis. B shows erosive damage (*red arrows*) at joint margins. C displays erosive change also, and more severe joint space narrowing plus marginal osteophytes. It is not possible from plain radiographs to determine whether the individuals concerned were experiencing pain, nor how severe any pain was. The osteoarthritic changes in C may represent comorbid osteoarthritis that preceded the onset of rheumatoid arthritis or may show secondary osteoarthritis following earlier erosive damage. Disease modifying treatments may reduce the progression of erosive damage in rheumatoid arthritis but do not always eliminate pain.

Comorbidities and Multimorbidity

Comorbid conditions may be associated with rheumatologic disease. Rheumatoid arthritis is associated with cardiovascular diseases, diabetes mellitus, and fibromyalgia. Rheumatologic conditions increase in prevalence with age. Therefore multimorbidity is common, with or without causal association between diseases. Multimorbidity is associated with increased pain severity and worse pain prognosis,[6] and contributes to frailty and loss of resilience to future health challenges. Concurrent morbidities might augment pain from rheumatologic conditions. Therefore treatment of comorbidities might improve pain outcomes. Morbidities or risk factors for future development may influence the choice of pain management strategy. Some, but not all, immunosuppressive therapies help with both cutaneous psoriasis and psoriatic arthritis. Comorbidities might be risk factors for adverse events from treatment, such as gastrointestinal bleeding on nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesic medication abuse. Morbidities that pose an anesthetic or surgical risk, such as hypertension or obesity, should be addressed before elective surgical intervention should be considered. A holistic approach is required to avoid interruption of pain management by intervening in acute medical needs. Morbidities may be painful or non-painful.

Rheumatologic conditions coexist with comorbidities, which further influence the pain experience. Fibromyalgia is a common accompaniment of both inflammatory and non-inflammatory rheumatologic conditions. The extent to which phenotypic similarities between rheumatologic conditions and fibromyalgia reflect shared mechanisms remains uncertain. Chronic widespread pain in people with hypermobility might be associated with comorbid fibromyalgia or central sensitization but might also be an indication of widespread abnormalities in peripheral nerve function. Fibromyalgia may be considered as a comorbid diagnosis, and also fibromyalgianess may be viewed as a continuous trait linked to pain mechanisms. Each may be classified or measured in people with rheumatologic conditions by questionnaires; the Symptom Severity Scale, which addresses fatigue, cognitive, and somatic symptoms, together with WideSpread Pain Index.[42]

Osteoarthritis is a common accompaniment of other rheumatologic conditions. Primary osteoarthritis (OA) is a prevalent condition. Similar to all non-fatal, incurable conditions, osteoarthritis increases in prevalence with age. Rheumatologic conditions may predispose patients to osteoarthritis. Hypermobility may be associated with joint trauma and inflammatory arthritis with erosive joint damage, each of which is a risk factor for secondary osteoarthritis.

Obesity is associated with osteoarthritis and increased pain. The association of body weight with osteoarthritis is multifactorial, partly based on genetic and biomechanical factors. Adipokines may contribute to augmented pain processing.[43] Reciprocally, where arthritis pain is a barrier to exercise, weight reduction may be difficult to achieve. Diabetes mellitus may be associated with obesity and is an autoimmune condition associated with inflammatory rheumatologic conditions. Diabetes mellitus is associated with increased pain, even in the absence of demonstrable neuropathy.[44] A negative association between osteoarthritis pain and hypertension has been attributed to the use of β-blocking medications,[45] although causality awaits demonstration by a randomized controlled trial.

Rheumatoid arthritis and systemic lupus erythematosus are associated with an increased risk of cardiovascular disease, which might be attributed to the effects of systemic inflammation or the adverse effects of treatments such as glucocorticoids or NSAIDs. Cardiovascular risk assessment tools incorporate rheumatoid conditions, including age, sex, smoking status, diabetes mellitus, hypertension, ischemic heart disease, and chronic kidney disease.[46]

Treatment History, Expectations, and Preferences

Assessment should include detailed documentation of treatment expectations and preferences. Expectations influence concordance with treatment plans and may contribute to analgesic efficacy or adverse events. A high expectation of benefit might facilitate placebo analgesia, whereas anticipating adverse events might contribute to nocebo responses. Expectations may be driven by the patient's understanding of the natural history and mechanisms of their disease and its treatment. The threat of pain is greater if pain is beyond an individual's comprehension or control. It is important to link the current biomechanical, structural, inflammatory, and neuronal mechanistic understanding of pain to the patient's experience. Explanations that clearly align treatments with the patient's informed understanding of the underlying mechanisms can enhance the therapeutic context and improve patient satisfaction.

A patient's previous treatment experience of pain strongly will influence their expectations from future treatment. In this respect, the patient's recollection may be the most important. Pain recollection might be unreliable beyond one week, whereas immunomodulatory drugs used for inflammatory arthritis often have a slow (several weeks) onset of specific analgesic benefits. Pain relief from high dose glucocorticoids may be rapid and easily appreciated by people with inflammatory arthritis. However, prospective pain documentation may be needed to understand the analgesic benefits of slower acting disease modifying anti-rheumatic drugs (DMARDs). Long term efficacy and side effect profiles might be preferable for DMARDs compared to glucocorticoids, even though the rapid analgesic benefit from glucocorticoids may be more easily appreciated. Previous treatment failure may create expectations of similar future treatment failure, and repeated treatment failure may lower expectations for all future treatments, not only those that have failed in the past. Treatments that are most likely to help and are least likely to cause adverse events should be selected for an individual. Patient expectations may differ from predictions from evidence-based prognostic tools, and this should be addressed to help patients choose optimal treatment.

Different individuals place different emphasis on treatment characteristics when making choices. Someone whose husband has just died from myocardial infarction may be averse to commencing an NSAID irrespective of their own personal risk. People with moderate to severe knee osteoarthritis generally place more emphasis on the likely analgesic efficacy rather than known adverse events.[47] Holistic assessment is needed to ensure that patients can make the best treatment decisions based not only on statistical models but also accounting for personal values and perspectives.

Pain Prognosis and Treatment Outcomes

Those people at the highest risk of poor outcomes stand to gain most from changes to their treatment. Assessment of a patient with a rheumatologic condition should lead to an understanding of likely pain prognosis, the likely impact of treatment on future pain, and the risk of treatment-related adverse events. Pain risk assessment overlaps with but does not equate to the risks of other outcomes, such as the risk of joint structural damage.

In populations undergoing usual care, worse knee pain at follow up may be predicted by a range of general and disease-specific risk factors. Across rheumatologic and non-rheumatologic conditions, being female, older age, higher body mass index (BMI), anxiety, depression, catastrophizing, and more widespread pain at baseline predicted worse pain outcomes, and indices of central sensitization, either using QST or questionnaires, also predict worse pain outcomes.[38,40] The average outcomes in a population conceal diverse pain trajectories in individuals. In osteoarthritis, pain progression is not inevitable, with pain deteriorating over time in some individuals but improving in others.[48] In people with early or established rheumatoid arthritis, subgroups have been identified whose pain may return to levels observed in non-diseased populations, whereas for others, pain may persist unchanged over several years.[32] Factors that predict the pain trajectory that an individual will follow overlap with those that predict persistent pain at follow up.

Specific interventions for rheumatologic conditions can change an individual's pain trajectory and outcome. Predictors of treatment response may differ, therefore, from predictors of pain outcomes in untreated populations. The raised acute phase might predict poor outcome in the absence of treatment for rheumatoid arthritis but predicts a more favorable pain trajectory on immunomodulatory treatment.[32] Joint space narrowing predicts worse outcomes in people with knee pain but predicts better outcomes in response to arthroplasty. Risk is therefore dependent on the treatment context, and we can anticipate that the adverse risk factors of today will become positive prognostic factors with treatments in the future.

Joint inflammation indices predict the analgesic benefits of immunomodulatory therapies in rheumatoid arthritis. DAS28 scores have been recommended by some for the selection of people who may be offered biologic immunomodulatory therapy. DAS28 requires careful interpretation because of the influence of non-inflammatory pain mechanisms. Randomized controlled trials in rheumatoid arthritis often require minimum thresholds of acute phase reactants and SJC to be met prior to treatment initiation.

An individual's risk factors and pain mechanisms may vary over time. This helps explain why a previously effective treatment might no longer be so, whereas another treatment that has previously failed might now help. For example, pain in early rheumatoid arthritis might respond well to immunomodulatory therapy, whereas in later disease, if central sensitization or joint damage becomes dominant, continuing to suppress inflammation might not relieve pain.

A single risk factor might make only a small contribution to pain outcomes, even if it displays highly significant associations in large cohort studies. For example, a high BMI predicts worse outcomes from joint replacement surgery, but people with high BMI can still gain important clinical benefits and should not be denied surgery.[49] Combinations of multiple risk factors may only explain a small proportion of treatment outcomes. For example, less than one-fifth of people destined to have poor outcomes from arthroplasty can be identified by a combination of currently known pre-surgical risk factors.[50] Risk factors should be discussed with the patient to help them minimize their risks while selecting what is appropriate for their care.

The analgesic response is not entirely attributable to specific effects and depends on contextual factors that might also be observed with placebo treatments. Only half of the total analgesic benefit experienced by the patient may be attributable to the specific effects of treatment.[51] The predictors of placebo response may differ from those of specific pharmacologic effects. This mixed mode of analgesic action challenges outcome prediction. For example, ultrasound evidence of synovitis may predict pain in people with knee pain,[31] but has little ability to predict the response to intra-articular glucocorticoid injection. Improved biomarkers of pain mechanisms are required to determine the effective targeting of mechanism-specific treatments.

Central mechanisms may predict worse pain outcomes in part by posing barriers to treatment response. A low mood might reduce treatment uptake or persistence, where the future seems hopeless. Anxiety and catastrophizing may reduce concordance with medical or physiotherapeutic interventions, where adverse events are feared, or where patients are concerned that by masking their pain, they will damage their joint. Sleep disturbance and chronic fatigue reduce motivation and the ability to engage in physical activity and therapies or to travel and attend to health care. Cognitive interference may impair the understanding or adherence to therapeutic plans. Multisite pain may compromise therapies targeting a particular joint, for example, by limiting mobility. Treating one joint may unmask the limitations of another. Identifying risk factors for poor outcomes as barriers to treatment benefit can reveal targets for interventions that might synergize with pain management.

Pain in rheumatologic conditions may persist for years, and long term benefits from analgesic medications are often unproven. Continued use of medications in those gaining little benefit exposes them to unnecessary risk of adverse events. Response to treatment should be assessed after an adequate therapeutic trial and should be confirmed before considering its continuation. What constitutes an adequate trial may vary between interventions. Two weeks might be adequate to evaluate response to an NSAID, whereas treatment with biologic DMARDs might be continued for up to six months before the benefit can be excluded, particularly if there are concomitant changes to glucocorticoid doses. Where treatment aims to reduce the frequency of pain flares, the duration of an adequate trial of treatment will depend on baseline flare frequency. For acute gout attacks, treatment should be titrated to achieve serum urate levels in the lower half of the normal range, and equivalent biomarkers are needed to satisfactorily reduce the risk of pain flares in inflammatory arthritis or osteoarthritis.

New treatments with different efficacy and risk profiles will increase the choices available to patients and their clinicians and increase the range of risk factors that need to be assessed. Pharmaceutical development of NGF inhibitors for osteoarthritis pain, for example, has identified risks from drug-induced rapidly progressive osteoarthritis, leading to the incorporation of risk screening tools such as large joint radiography into developmental treatment pathways.[18]

Management

General Principles

Box 46.1 summarizes the key management recommendations from recent guidelines for health professional contributions to rheumatologic pain management.[52–54] Guidelines recommend holistic patient assessment and a stepped care approach, incorporating steps of increasing treatment intensity and cost from education and self-management through specialist and multi-disciplinary care. A personalized approach depends on an individual's risk factors, needs, and values. Not all treatments are necessary or appropriate for all patients. A personalized management plan guided by shared decisions can help in implementing this approach.

• BOX 46.1 Health Professional Management of Pain in Rheumatologic Conditions

Education:

- Educational materials, brochures/online resources encouraging to stay active, sleep hygiene guidelines
- Psychoeducation by a health professional
- Self-management interventions; online/face to face

Physical activity and exercise:

- Advice to stay active
- Physiotherapy; individually tailored graded physical exercise or strength training
- Multi-disciplinary intervention; cognitive behavior therapy addressing fear of movement and catastrophizing

Occupational therapy, orthotist, orthopedic shoemaker:

- Splints, braces, gloves, sleeves, insoles, and shoes
- Daily living aids: e.g. tin openers
- Assistive devices: e.g. cane, rollator
- Ergonomic adaptation at home/workplace

Psychological or social interventions:

- Basic social and psychological management support
- Referral to a psychologist, social worker, self-management support program, cognitive behavior therapy

Sleep interventions:

- Basic education; sleep hygiene
- Referral to sleep therapist/program or specialized sleep clinic

Weight management:

- Dietitian, psychologist, community lifestyle services, or bariatric clinic/surgery

Pharmacologic and joint-specific pain:

- Advice on prescribed and over-the-counter pain relief
- Refer for medical advice if concerns about safe/effective use or if additional pharmacologic treatment may be indicated

Multi-disciplinary treatment:

- If more than one treatment option is indicated or if monotherapy failed

Box 46.1 summarizes the key management recommendations from the EULAR guidelines for health professional contributions to rheumatologic pain management.[52] Comparable guidelines have been issued by the American College of Rheumatology.[53] The Osteoarthritis Research Society International (OARSI) has published guidelines using evidence for knee, hip, or generalized osteoarthritis, including benefits in outcomes additional to pain.[54] All patients should be offered personalized advice and guidance, beyond which a stepped care approach provides treatment access to those who may most benefit. Individuals or professional groups may have particular skills in specific treatment areas, although treatment may be delivered by a range of professional and non-professional team members.

Optimal management requires consideration of the nature and impact of rheumatologic pain alongside other symptoms that the patient seeks to address and risk factors for future pain progression. Realistic expectations should be encouraged based on evidence-based information on likely outcomes for individuals with or without treatment. Decisions to initiate treatment depend on individual benefits balanced against adverse events and risks, focusing on the patient's perspective. Response to any single treatment may vary between individuals, and treatment should be continued where benefits outweigh the risk. Modifiable risk factors such as low mood, anxiety, or obesity might be indications for treatment in their own right and improve pain prognosis. The risk of gastrointestinal bleeding on NSAIDs can be reduced by co-prescription of proton pump inhibitors, and that of osteoporosis on glucocorticoids can be reduced by bisphosphonates in the context of adequate calcium and vitamin D intake.

Different pain mechanisms and qualities in an individual may demand a combination treatment. Interventions might aim to suppress constant, ongoing pain or to prevent, suppress, or abort intermittent pain episodes. Oral NSAIDs can relieve rheumatologic pain, but their use may be limited by the patient's baseline cardiovascular, gastrointestinal, or renal risks. Opiate analgesics may acutely relieve rheumatologic pain. However, despite the absence of evidence of sustained analgesic benefits from opioids in inflammatory arthritis, their use progressively increased from 2002 to 2015.[55] Many patients choose to use analgesic medications on an "as required" basis, according to hour-to-hour variations in symptoms, pre-emptively to facilitate a specific activity or to help manage a pain flare. Such intermittent treatment might help optimize the balance between benefit and risk, and randomized controlled trials have not demonstrated clear superiority of regular over "as required" analgesic use. However, "as required" usage should be strongly discouraged for slow-acting treatments, such as DMARDs, urate-lowering therapies, or antineuropathic analgesics.

Some treatments might effectively reduce pain across multiple diagnoses, whereas others have demonstrable efficacy only for a single disease. Intra-articular glucocorticoid injections may reduce pain in rheumatoid arthritis or osteoarthritis. Systemic glucocorticoids might reduce pain in rheumatoid arthritis,[56] but are not recommended for osteoarthritis. TNFα blocking antibodies might reduce pain from rheumatoid arthritis or psoriatic arthritis, whereas IL-6 blockade might reduce pain only in RA, and IL-17 blockade only in psoriatic arthritis (Table 46.1).[57] For some conditions, specific treatments are not available, and generic pain management approaches should be adopted. Hypermobility syndrome is determined by genetic variants that cannot be modified by specific treatments. Quadriceps strengthening may improve hypermobility-associated anterior knee pain, and strategies developed for people with fibromyalgia may be helpful, although exercises aimed at *increasing* mobility should be avoided by these people.

Exercise therapies are commonly prescribed and may reduce rheumatologic pain, improve strength, balance, and endurance, reduce frailty and falls, and improve general health outcomes. Exercises may need to be individualized based on patient comorbidities. Formal knee exercises may need to be performed in the presence of significant hip disease. Aerobic exercise might be precluded in patients with unstable angina, although increasing aerobic fitness might ultimately reduce cardiovascular risk. Rheumatologic treatments are often complex and might be challenging for people with cognitive impairment or if motivation is compromised by a low mood. Attendance in group exercise may be precluded by agoraphobia or personality disorders.

Osteoarthritis

Randomized controlled trials in osteoarthritis have focused predominantly on major weight-bearing joints such as the knee or hip. Evidence may be less robust for the management of hand OA pain, and although shared principles of analgesia and exercise might be valid, therapies may need adaptation to the particular

TABLE 46.1 Targeted Immunologic Therapies for Inflammatory Arthritis

Molecular Target	Pharmaceutical Agent	Rheumatologic Condition	Direct Actions on Peripheral Sensory Nerves
Tumor Necrosis Factor-α	infliximab, etanercept, adalimumab, certolizumab, golimumab	Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis	Sensitizes voltage gated sodium channels[70] Upregulates NaV1.7 currents[71] Increases gene expression; CGRP, adrenomedullin, CCL2, MMP9,[72] Nav1.6,[73] Nav1.7,[74] BDNF[75] Increases neurite outgrowth[76]
Interleukin-1 β	anakinra	Rheumatoid arthritis	Increases CGRP expression[77] Increases CGRP,[77] and SP release[78]
Interleukin-6	tocilizumab, sarilumab	Rheumatoid arthritis	Increases TRPV1 and NK1 receptor expression[79]
Interleukin-17	secinumab, ixekizumab, brodalumab	Psoriatic arthritis, Ankylosing spondylitis	Increases axonal outgrowth and mitochondrial function[80]
Interleukin-12/23	ustekinumab, guselkumab	Psoriatic arthritis	Unknown
CD20 (B cell depletion)	rituximab	Rheumatoid arthritis, Systemic lupus erythematosus	Unknown
CD80/86 (T cell costimulator)	abatacept	Rheumatoid arthritis	Unknown
JAK kinase/STAT3	baricitinib, tofacitinib	Rheumatoid arthritis, Psoriatic arthritis	Mediates TNFα induced gene expression[73]

Direct effects on dorsal root ganglion neurons of molecular targets for biologic DMARDs (bDMARDs) and targeted immunomodulatory agents. The predominant analgesic action of bDMARDs is because of the suppression of peripheral inflammation and may be attributed to the suppression of the release of other sensitizing agents. However, molecular targets may themselves sensitize peripheral nociceptors, and direct effects on nerve function may precede the secondary effects of immune suppression. Biologic agents have very low penetration across the blood-brain barrier, such that their analgesic actions are likely to be peripherally mediated. Inhibitors of JAK kinase/STAT3 might have additional effects, for example, on glial cells within the central nervous system.

needs of different joint groups. International guidelines on the management of OA recommend core treatments for arthritis education and structured land-based exercise programs comprising strengthening, cardiovascular fitness, balance training, and neuromuscular control, or mind-body exercises such as tai chi or yoga.[54] These core treatments aim to improve both pain and functional capacity. Meta-analysis of exercise trials suggests that mind-body exercise might be more effective than muscle strengthening exercises for improving knee pain.[58] However, further research is required to determine whether different treatment approaches may be more acceptable or effective for different individuals.

Core exercise therapies may be supplemented by aquatic exercise, gait aids, or self-management programs in people at high risk of poor outcomes. In addition, they might be offered analgesic medications such as topical NSAIDs or oral NSAIDs, if these are not contraindicated, together with proton pump inhibitors for gastroprotection. Topical capsaicin may also provide clinically important pain relief from knee or hand OA, with similar overall efficacy as topical NSAIDs, although different people might respond better to one or other of these medications.[59] Current evidence does not allow accurate prediction of which analgesic medications will best help which patient, and if the first tried intervention is ineffective, a second treatment should be considered. Intra-articular corticosteroid injection may reduce OA pain, often for some weeks, but cannot be self-administered and can rarely be associated with important adverse events, such as accelerated structural damage.[60] Other analgesic medications have limited specific benefits for osteoarthritis pain. Randomized controlled trials have not unequivocally demonstrated the benefit of paracetamol in osteoarthritis, which is less effective for OA pain than are NSAIDs. Paracetamol has a narrow therapeutic window above which liver toxicity may be significant as well as other adverse events comparable to those observed with NSAIDs.[61] Oral or transdermal opioids do not have evidence of sustained benefits for OA pain, and risks of nausea, constipation, cognitive impact, falls, and dependency may outweigh any benefit. There is an urgent need for more effective medical treatments for OA pain, several of which are in development.[18]

Where core and supplemental interventions do not adequately control osteoarthritis pain, intra-articular hyaluronic acid injections might be considered as also may combination of exercise with cognitive behavior therapy.[54] However, failure of conservative pain management approaches may indicate a need for surgical intervention. Better pre- and perioperative pain control, lack of musculoskeletal comorbidities including fibromyalgia, low indices of central sensitization, low BMI, more joint space narrowing, good mental health, and low catastrophizing predicted better outcomes from large joint arthroplasty. However, these factors explain only a small proportion of the variation in outcome and should be viewed as targets to improve outcome rather than hurdles that must be overcome before surgery is offered. For appropriately selected

patients, pain improvement following arthroplasty is usually pronounced, particularly with hip replacement surgery. However, up to 20% of people undergoing total knee arthroplasty continue to suffer from pain.[62] Relieving pain alone might not be sufficient to enable people to return to their valued activities. Adjunctive therapies, addressing fear avoidance, low mood, and comorbidities, play important roles.

Inflammatory Arthritis

Optimal management of pain in inflammatory arthritis can reduce the burden of symptoms and enable patients to better manage their inflammatory disease. People with inflammatory arthritis report major concerns with pain, fatigue, stiffness, and disability, whereas physicians often pay more attention to biomarkers of inflammation or joint damage. This discrepancy has been associated with worse outcomes after treatment.[63] The aim of modern DMARDs is to induce and maintain inflammatory disease remission, but many patients continue to experience intermittent flares or persistent low-grade inflammation. Non-inflammatory pain mechanisms may persist despite resolution of inflammation, and improvements in pain on treatment, although clinically important, may not be complete, even when inflammation is completely suppressed.[32]

Rheumatoid Arthritis

Suppressing inflammation can reduce pain in active rheumatoid arthritis,[6] and reduce stiffness and joint swelling. Immunosuppressive therapies can slow or stop structural damage and are referred to as DMARDs. A wide variety of DMARDs are available, with high-quality randomized controlled trial evidence of clinically important benefits for pain. These include conventional synthetic DMARDs such as methotrexate and targeted biologic agents including TNF-α blockers, B cells (rituximab) or T cells (abatacept) directed therapies, IL-6 blocking antibodies (tocilizumab, sarilumab), and small molecule JAK/STAT kinase inhibitors (e.g. baricitinib, tofacitinib; Table 46.1).[64] Each significantly increases the risk of infection, and several may have potential liver or hematologic toxicity. Regular blood monitoring during treatment may reduce risks by detecting adverse events before they become clinically apparent. The requirement for subcutaneous or intravenous delivery of biologic agents, need for monitoring, and cost may necessitate provision through secondary care services. Immunosuppressive therapies usually do not have immediate benefit, and depending on the chosen agent, treatment for up to six months may be required to definitively assess the benefit. Pain may be severe, and there is both a practical and ethical imperative to relieve pain before these slow-acting treatments can take effect.

More rapid suppression of inflammation at disease onset or during flares might be achieved by glucocorticoids. These may be administered by local (e.g. intra-articular) injection or systemically by tablet, intramuscular injection, or intravenous infusion. Systemic glucocorticoids administered by any of several routes may provide effective analgesia for inflammatory pain in rheumatoid arthritis and reduce stiffness, joint swelling, and fatigue. Adverse events with short-duration treatment are usually not troublesome, although high doses of glucocorticoids can precipitate or destabilize diabetes mellitus or induce psychosis. Short courses of low dose systemic glucocorticoids, such as prednisolone (7.5 mg daily or less), may be less likely to cause problems but might be less effective at reducing pain. Long term glucocorticoid use is associated with reduced symptomatic benefit and increased risk of adverse events, some of which can be mitigated by concomitant medication (e.g. bisphosphonates to reduce osteoporosis risk). Patients who experience a good symptomatic response to high dose glucocorticoids shortly after disease onset might be reluctant to engage with maintenance DMARD treatment in light of the latter's slow onset of (and therefore less noticeable) symptomatic benefit and potential for adverse events. However, long term glucocorticoid use itself has high risk and low efficacy and does not retard structural damage in established inflammatory arthritis. DMARDs should be introduced to permit the eventual withdrawal of any initial glucocorticoid therapy.

NSAIDs may also reduce inflammatory pain in rheumatoid arthritis and improve joint stiffness. They have the advantage of ready availability and may be used "as required." Topical NSAIDs or topical capsaicin may be beneficial in rheumatoid arthritis, even in the absence of concurrent osteoarthritis, although evidence is less robust than in osteoarthritis. Glucocorticoids also inhibit cyclo-oxygenases, and concurrent use of NSAIDs with glucocorticoids substantially increases the risk of gastrointestinal bleeding. However, concurrent NSAIDs may provide analgesic benefits over and above the analgesia from low dose glucocorticoids below 7.5 mg prednisolone daily. The peak age of onset of rheumatoid arthritis is now >50 years, and comorbid cardiovascular or renal disease or anticoagulant treatment may limit the number of people who can benefit from oral NSAIDs.

Other Forms of Inflammatory Arthritis

Pain in psoriatic, enteropathic (e.g. ulcerative colitis and Crohn's disease), reactive arthritis, and ankylosing spondylitis displays similar characteristics, periodicity, and responds to many similar treatments as rheumatoid arthritis pain, although with some important differences (Table 46.1). The molecular pathways of inflammatory pain differ between diseases. For example, IL-17 blockade may effectively reduce pain in psoriatic arthritis but is not currently recommended for rheumatoid arthritis.[64] Different forms of inflammatory arthritis may have different comorbidities, and treatments should be selected to reduce the symptoms and impact of comorbidities. For example, TNF-α inhibitors may improve spinal and peripheral joint pain and improve skin disease in psoriatic arthritis. Seronegative inflammatory arthritis may be associated with uveitis, sometimes sight threatening, and a difficult balance may be needed between symptomatic benefit from some biologic agents and their potential to precipitate or aggravate ocular disease. TNF-α inhibition has not been conclusively shown to slow the progression of bone structural changes in inflammatory spinal disease, but excellent symptomatic benefit alone justifies the associated risks of immunosuppressant therapies.

Non-inflammatory Pain and Inflammation Nonselective Interventions in Inflammatory Arthritis

Even when inflammatory disease is in remission, people with inflammatory arthritis may continue to experience unacceptable pain. An acutely painful joint in someone whose arthritis is otherwise well controlled should always raise the relatively rare possibilities of other diagnoses, such as infection or insufficiency fracture. Chronically persistent and disabling pain is reported by up to 30% of patients with rheumatoid arthritis,[32] or psoriatic arthritis[65] despite objective evidence of inflammatory disease remission. This disappointing average outcome conceals subgroups in which pain remits to levels reported by normal populations, but also other subgroups who appear to gain little analgesic benefit from the introduction of DMARD treatment.[32] Persistent non-inflammatory

pain is, therefore, a major problem for these patients. Furthermore, the assessment of inflammatory disease activity and clinical scores used to determine the response to immunomodulatory treatments are strongly influenced by pain.[26,30] Pain improvement may be necessary to persuade patients and clinicians that inflammatory diseases are adequately controlled and avoid unnecessary escalation and risks from immunosuppression.

Persistent "non-inflammatory" pain may be because of pre-existing morbidities or be a consequence of earlier active inflammatory disease. Half of the patients presenting to secondary care with early rheumatoid arthritis already have radiographic osteoarthritis of the hands or feet.[66] Up to a third of people with established rheumatoid arthritis, psoriatic arthritis, or spondylarthritis may satisfy the classification criteria for the diagnosis of fibromyalgia.[67] Fibromyalgia diagnosis may be only the tip of the iceberg, and fibromyalgianess affects many people who do not meet the fibromyalgia classification criteria for a formal diagnosis.

Treatments recommended for primary fibromyalgia or osteoarthritis should be offered to people with inflammatory arthritis when diagnosed with these comorbidities. Indeed, pain management strategies used in non-inflammatory pain conditions can be helpful for people with inflammatory arthritis, even in the absence of a comorbid diagnosis. Care from health professionals should use a patient-centered framework with a personalized management plan, pharmacologic and joint pain-specific treatments, and a multi-disciplinary approach.[52,53] Strong research evidence supports the use of education, aerobic exercise, cognitive behavior therapy, and weight loss in obese individuals. In addition, there is some evidence for benefit from strength training, hypnotherapy, biofeedback, balneotherapy, yoga, tai chi, neuromodulation, acupuncture, chiropractic, manual, and massage therapy.

Comorbid inflammatory arthritis raises additional concerns in people with fibromyalgia or osteoarthritis. Each of these conditions may be associated with "pain flares," and patients and clinicians may struggle to understand whether any particular flare indicates a need to escalate anti-inflammatory treatment or to pursue more intensive pain management strategies. Misattribution of pain to non-inflammatory causes might prevent access to effective treatments, whereas repeated courses of high dose glucocorticoids are inappropriate for fibromyalgia or osteoarthritis pain flares. Engagement with chronic pain management interventions may be limited if patients believe that their pain will resolve once they are established on effective DMARD treatment. Graded physiotherapy may be helpful for osteoarthritis and fibromyalgia, but an increase in pain during an exercise program may indicate a need for further individual assessment of inflammatory disease activity.

In summary, treatments for fibromyalgia and osteoarthritis are not contraindicated in patients with inflammatory arthritis, and many modalities have benefits for both inflammatory and non-inflammatory pain. Many patients require many months of DMARD treatment adjustments before inflammatory disease enters remission. Early and effective management of non-inflammatory pain should aim to minimize suffering during this period, reduce the risk of chronic pain and equip the patient for effective self-management in the long term.

Gout and Pseudogout

The key aims of gout management are to relieve acute pain during an attack and prevent future attacks by controlling serum urate levels.[68] Prevention is not currently possible for pseudogout, for which management focuses on treating acute attacks.[69] Gout is associated with significant renal, cardiovascular, and metabolic comorbidities that may complicate treatment and require management in their own right.

Rapid pain reduction during acute attacks of gout or pseudogout may be achieved using colchicine, NSAIDs, and/or glucocorticosteroids. Colchicine inhibits microtubule function, thereby reducing leukocyte degranulation. Microtubules also regulate gastrointestinal epithelial and neuronal function, such that colchicine may also often cause diarrhea, with neuropathy, if use is prolonged. NSAIDs are similarly effective for treating acute crystal-induced pain. However, NSAIDs may be contraindicated for people whose gout is associated with significant renal disease, a cause of hyperuricemia, or metabolic syndrome and associated cardiovascular disease. By intra-articular injection or systemic administration, glucocorticoids may also rapidly reduce pain during an acute crystal attack. However, their use requires the prior exclusion of joint infections. Despite the severity of pain during crystal attacks, strong opioids are usually unnecessary because more effective analgesia can be achieved with specific therapies directed at inflammatory mechanisms.

In addition, to acute gout attacks, management aims to reduce the risk of recurrence. Recognized precipitants of gout attacks may be avoided, such as alcohol intake or medication changes such as thiazide diuretics. However, long term urate-lowering treatments, such as allopurinol, should be considered for those at high risk of future attacks, such as those who have experienced more than a single attack or those with very high serum urate levels. With effective urate-lowering therapy, complete prevention of acute attacks is possible. Disappointingly, many patients continue to experience repeated attacks of gout over many years. The reasons for this are complex. A lack of understanding that treatment offers control rather than cure might lead people to discontinue once the patient feels well. Reduction in serum uric acid concentrations on medication may vary considerably between individuals, and dosage titration is required to achieve serum urate concentrations in the lower half of the normal range if acute attacks are to be prevented. Acute attacks may be triggered by either increasing or *decreasing* urate levels, and patients may not understand that an attack shortly after starting treatment, while serum urate levels are decreasing, does not predict long term treatment failure.

Conclusions

Rheumatologic conditions are commonly associated with both acute and chronic pain. Many have clearly defined pathologic mechanisms, enabling specific treatments to offer rapid and effective pain relief. However, pain in rheumatologic conditions is multifactorial and complex, and suppression of underlying disease often does not eliminate pain. Advances in targeted immunosuppressive therapy have made inflammatory disease remission a realistic goal for most patients with rheumatoid arthritis. However, non-inflammatory pain mechanisms remain resistant to treatment, and new treatments are urgently needed. More could be gained from existing therapies by careful and timely selection and targeted access for those most likely to benefit. The multitude of potentially useful pain management strategies offers hope to those seeking help, but some feel lost and unable to find the best way forward. This journey is shared by patients, family members, friends, and professionals. Rheumatologic pain management demands a personalized approach based on the individual's values and aspirations and a clear explanation from healthcare professionals regarding their evidence-based understanding of pain mechanisms, treatment benefits, and risks.

Key Points

- People with rheumatologic conditions suffer from diverse pains, which may vary in severity, quality, and impact over time, and between individuals.
- Multiple and changing mechanisms underlie rheumatologic pain, including peripheral nociception and nociplastic pain associated with mechanisms in the central nervous system.
- Pain in rheumatologic conditions is often linked to comorbid symptoms of fatigue, stiffness, disability, low mood, and anxiety. Pain should be managed alongside these other symptoms to maximally improve the quality of life.
- Pain mechanisms and, therefore, some treatment recommendations overlap between inflammatory and non-inflammatory rheumatologic conditions and with other non-rheumatologic chronic pain.
- General principles of rheumatologic pain management reflect those in other chronic pain conditions, benefiting from a personalized, multi-disciplinary approach proportionate to the needs of the patient.
- Treatments targeting molecular pathways of specific immunity can effectively reduce pain in inflammatory rheumatic conditions such as rheumatoid arthritis, but residual non-inflammatory pain remains a major treatment challenge.
- Intermittent pain, often severe and unpredictable, has a major impact on people with rheumatologic conditions. In gout, maintenance urate-lowering therapy can prevent flares if adequately implemented, but adequate flare prevention in other rheumatologic conditions requires further research.
- Painful and non-painful comorbidities are common in people with rheumatologic conditions and should inform treatment choices to maximize benefits for the person as a whole and to minimize the risks of adverse events.
- Individuals have diverse values and might place more or less emphasis on pain and its relief, other symptoms, cost and inconvenience of treatment, and other potential or experienced adverse events. Treatment should be tailored to the individual's needs and values.
- Pain management is a moral and personal necessity that should not be delayed while establishing optimal disease modification, which may take several months.

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Pain Management in Patients With Comorbidities

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Introduction

Pain is defined by the International Association of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage."[1] Given that pain is not only a symptom but also an independent disease, it is highly likely that patients with chronic pain may also have other medical comorbidities and disorders that will influence the scope of treatments that are recommended. In any patient with chronic pain, the severity, frequency, and tolerance to the condition are variable and are influenced by a variety of factors, including one's cultural background, expectations, behaviors, and physical and emotional health. In patients with comorbid conditions such as renal and hepatic diseases, diabetes, and the elderly, an understanding of how these conditions may influence pain treatment is of utmost importance. The appropriate selection of non-pharmacologic, pharmacologic, and interventional treatments based on the underlying comorbid conditions has the potential to improve physical functioning, emotional wellbeing, and overall quality of life. The scope of this chapter is to understand how pain management strategies need to be understood and tailored to specific comorbid medical conditions, including renal disease, liver disease, diabetes, and the frail/elderly population.

Renal Disease

Prevalence

Chronic kidney disease (CKD) is a global public health problem that is increasing in incidence and prevalence and is associated with poor patient outcomes and high medical costs.[2] CKD is defined as the progressive and gradual loss of the kidneys to concentrate urine, excrete wastes and metabolites, secrete hormones, and conserve electrolytes. There is a distinction between CKD and end stage renal disease (ESRD), which is the deterioration of kidney function to the point where renal dialysis or transplantation is required for survival. Patients with CKD and ESRD experience a high severity and prevalence of physical symptoms related to their diseases. The symptom burden in these populations is greater than that of the general population, and despite this well-described complication, many patients have underrecognized, underestimated, and undertreated symptoms related to their CKD and ESRD.[3–5] Pain is one of the most common symptoms encountered in CKD and ESRD, with the reported prevalence of pain ranging from 30 to over 58%.[6–9] In patients with ESRD who are on hemodialysis (HD) or peritoneal dialysis (PD), the prevalence of acute and chronic pain has recently been shown to be up to 80%.[10] Of these patients who report pain, it has been shown that over half report pain as moderate to severe in intensity.[8,9,11,12]

Etiologies

Similar to the underlying disease processes present in CKD and ESRD, the pain experienced by patients with kidney disease is often multifactorial. Etiologies of pain can be either straightforward or complex and related to a multitude of issues (Table 47.1). Symptoms can be caused as a direct result of the primary underlying kidney disease process, such as pain related to autosomal dominant polycystic kidney disease, or they can be related to associated underlying systemic and comorbid diseases such as diabetes, peripheral vascular disease, and various musculoskeletal processes.[7] Pain may also be experienced as a direct result of HD or PD procedure itself.[10,12] It is also important to remember that additional pain related diagnoses such as anxiety, depression, and sleep problems may coexist with the chronic pain syndromes experienced by CKD/ESRD patients and that these conditions may feed into the challenges that coincide with treating chronic pain in these populations.

As in any patient with acute or chronic pain, determining the type and severity of the pain can provide an excellent roadmap for outlining treatment plans. Listening to the patient about their symptoms and experiences surrounding their pain provides a great opportunity to provide them with compassion and validation of the significance of their problem and is an important piece of the therapeutic relationship.

Acute and chronic pain can be classified as nociceptive, neuropathic, nociplastic, or mixed pain. By definition, nociceptive pain arises from actual or threatened damage to non-neural tissue and results from the activation of nociceptors, while neuropathic pain is a clinical description that requires a definite lesion or a specific disease process that affects the somatosensory nervous system. The persistence of nociceptive stimuli can lead to several functional and structural changes in the central nervous system, known as central sensitization.[13] Many chronic pain conditions are characterized by central sensitization, widespread pain, and altered descending pain modulation.[14] The IASP has recently introduced a new term, nociplastic pain, defined as conditions that arise from altered nociception, without clear evidence of actual or threatened

TABLE 47.1 Pain Origins in Chronic Kidney Disease and End Stage Renal Disease

Pain Origin	Examples
Intrinsic Kidney Pathologies	Calciphylaxis Renal osteodystrophy (bone pain) Limb ischemia because of dialysis access steal syndrome Dialysis related amyloid arthropathy
Underlying or Comorbid Disease Processes	Autosomal dominant polycystic kidney disease Urinary tract infections Vascular peripheral neuropathy Diabetic peripheral neuropathy Amyloidosis Phantom limb pain Dermatologic conditions Malignancy Osteoporosis
Dialysis Related	AV fistula/graft surgical creation Needlestick cannulation of HD AV access Instillation of PD fluid PD associated peritonitis, low back pain Muscle cramping from dialysis ultrafiltration Pruritis Headache Chest pain associated with intradialytic hypotension Dyspnea Infected HD catheter
Pain Unrelated to Kidney Disease	Osteoarthritis Malignancy Degenerative disc disease Radiculopathies Migraines Gout Fibromyalgia Restless leg syndrome Entrapment neuropathies

Clinical Presentation and Assessment of Pain in CKD/ESRD.

tissue damage or lesions, or disease of the somatosensory nervous system. Patients with ESRD may suffer from nociceptive, neuropathic, nociplastic, or mixed pain states. Ascertaining the mechanism of chronic pain is essential in the choice of mechanism-based analgesic therapies.[15,16]

A thorough and complete pain assessment includes determining several attributes that contribute to acute and chronic pain, such as pain severity, pain quality (described in the previous paragraph), eliciting and attenuating factors, impact of pain on daily activities and physical functioning, pain interference with mood and sleep, and effects of pain on quality of life. No instruments have been specifically designed and validated for pain assessment in CKD/ESRD patients. However, several approaches can be used. One-dimensional scales are instruments used to identify pain severity, while multidimensional scales can be utilized to reflect the biopsychosocial model of pain that integrates social and psychological paradigms with the biologic mechanisms of pain.

The most commonly used one-dimensional scale for pain assessment is the 11 point numeric rating scale (NRS), where zero indicates no pain and ten is the worst imaginable pain, and the 10 cm (100 mm) continuous visual analog scale (VAS), which is anchored by the two verbal descriptors for each extreme ("no pain" and "pain as bad as it could be"). Many of the same assessment tools that exist for patients with non-kidney disease pain are valid and reliable in the CKD/ESRD population. The McGill pain questionnaire (MPQ) and the brief pain inventory (BPI) are the most common multidimensional scales used to assess pain. The MPQ has been in use since 1975 and is a widely used instrument to evaluate pain and helps determine both quantitative and qualitative aspects of pain, such as location, grade, temporal characteristics, and intensity.[17] The BPI, initially developed for cancer patients but validated for use in chronic non-cancer pain, uses an 11 point NRS for pain intensity, requests the patient to draw the site(s) of pain on a body diagram, and uses an 11 point NRS to assess pain interference in seven domains, including general activity, mood, walking ability, work, relations with other people, sleep, and enjoyment of life.[18]

Assessment tools such as the modified Edmonton symptom assessment system (m-ESAS v. 2),[19] and palliative care outcome scale-renal (POS-renal)[20] are renal-specific screening tools that may be more appropriate for routine clinical screening for pain in renal patients. These assessments identify the presence of pain and provide opportunities for discussions about appropriate palliative and supportive care treatment options.

Barriers to Pain Management in Kidney Disease

As mentioned previously, chronic pain is very common in patients with CKD and ESRD. However, it has historically been underrecognized and often poorly managed. It is well known that poorly controlled pain leads to decreased quality of life, poor physical functioning, reduced mobility, increased healthcare utilization, and longer hospital stays.[16] Numerous reasons have been reported for insufficient pain management in CKD and ESRD, including inadequate pain assessment, concerns about analgesic-related adverse effects, and misconceptions.[3,5,16]

As described in the previous section, an adequate pain assessment requires an accurate medical history, thorough physical examination, and the application of validated tools for the identification of pain intensity and quality. The presence and severity of pain should be regularly assessed in patients with CKD and ESRD, and if applicable, during each HD session. Pain is generally undertreated in patients with CKD and ESRD because of the fear of the potential toxicity of analgesic drugs. Overtreatment, overdose, and inadequate analgesia can result from inappropriate dosing of non-opioid and opioid analgesics. Unfortunately, quality data or guidelines on the pharmacokinetics, clinical efficacy and safety of many common analgesics in this population are lacking. Indeed, the translation of pharmacologic pain management methods used in non-CKD/ESRD populations can be dangerous, as patients with CKD and ESRD have reduced renal function and altered pharmacokinetics.[21] Alterations in metabolism and excretion may lead to significant adverse toxicities and side effects. Renal dose adjustments are required for most analgesics.

Setting Expectations

At the initiation of any pain management treatment program, the provider must discuss with the patient the expectations of therapy. These expectations should include the identification of reasonable therapeutic goals, including the level of pain that is acceptable for

a patient's quality of life, the risks and benefits of the treatment(s), the potential duration of pharmacologic therapy, and if applicable, the components of a pain contract for continued care. The overall goal of both immediate and long term pain management should be to improve the functional status. Moreover, a discussion that the patient should not expect to be pain-free is of importance and that a reasonable expectation should be that pain may not be completely resolved or controlled and that a 30% reduction in pain symptomology is often identified as clinically meaningful.[22]

Pain Management Approach in Patients With CKD and ESRD With or Without Hemodialysis

General Principles

Pain treatment should be tailored to each individual according to the type and severity of pain. In general, non-pharmacologic options should be used first. Non-pharmacologic treatment options can be broadly categorized as psychosocial/behavioral interventions (e.g. cognitive behavior therapy (CBT), mindfulness) and physical interventions (e.g. exercise, physical therapy, yoga, acupuncture, electrical stimulation). Although most of these have not been specifically tested in CKD/ESRD, they have been proven to be effective in other chronic pain states and thus provide an encouraging approach for the treatment of pain in this population, either alone or as an adjunct to pharmacologic treatment.

Pharmacologic analgesic therapy should be based on the type of pain, severity of pain, and when the benefits of medications are cautiously weighed against possible side effects, drug-drug interactions, and coexisting medical morbidities. It is recommended that patients initiate therapy on a minimal dose of an analgesic medication and up-titrated slowly based on response and tolerance with very close monitoring for side effects or adverse events. An opioid-sparing approach is recommended in most cases.

Non-pharmacologic Therapies

The non-pharmacologic approach is the first step in pain management. In particular, in patients where drugs are not free of risks, non-pharmacologic techniques should be encouraged. Non-pharmacologic interventions include biofeedback, CBT, massage, and physical therapy/exercise programs.

CBT has become a well-established and accepted treatment for chronic pain in the general population. Robust evidence from a meta-analysis of 35 trials (>4700 patients) supports its efficacy for improving chronic pain symptoms and pain related physical disability in the general population. However, the effect size may be small, and the long term effects are not durable.[23] In the CKD/ESRD population, CBT is effective in improving depression, but its effect on pain has not been tested.[24] CBT has been shown to be effective in the general non-cancer chronic pain population and is based on concepts surrounding poor self-management skills, self-efficacy, and coping skills, which typically exist in this patient population. There is a strong premise that CBT may be a successful non-pharmacologic pain management strategy.

The potential benefits of complementary and alternative medicine have not been adequately investigated in patients with CKD/ESRD. These interventions include relaxation techniques, mindfulness, and acupuncture. A systematic review of randomized control trials investigating the effect of relaxation techniques in >400 patients with chronic pain in the general population found no significant benefit in reducing pain. However, the studies were of low quality, and thus the data are not conclusive at this time.[25] In HD patients, two small studies have shown that relaxation techniques may improve pain intensity and health-related quality of life.[26,27] Mindfulness-based techniques including meditation, which involves focusing the mind on experiences (e.g. sensations, emotions, thoughts) in the present moment, have shown some promise in improving pain in the non-ESRD population.[28] Moreover, a recent pilot study demonstrated that a brief, individualized, chairside mindfulness meditation intervention was feasible and acceptable for HD patients.[29] A recent Cochrane analysis evaluated 24 studies on various types of acupuncture in patients with CKD. There is a paucity of evidence on the efficacy of acupuncture for fatigue, depression, sleep disturbance, and uremic pruritus in HD patients. Moreover, data on possible acupuncture-related harm are lacking. Therefore no conclusions may be drawn on its safety.[30]

In the multimodal approach to chronic pain, invasive interventional pain techniques may potentially play a role in treating pain refractory to conventional pharmacologic treatment or to reduce the dose of analgesics in patients with CKD/ESRD. There is a paucity of literature on this topic. However, spinal cord stimulation (SCS) could be useful in HD patients suffering from peripheral vascular disease, stump pain after amputation, and painful diabetic neuropathy (PDN), but current guidelines only support a weak recommendation.[31]

Pharmacologic Therapies

The World Health Organization ladder for analgesic pain control, originally created for cancer pain treatment, has been validated for use in the CKD/ESRD population.[32] The modified ladder uses a three-step approach for pain management. Mild pain is generally treated in step 1 using non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Step 2 treats moderate pain with the addition of mild or weak opioids such as tramadol, low dose oxycodone, and low dose hydromorphone. Step 3 initiates higher-dose opioids, such as higher doses of oxycodone/hydromorphone, fentanyl, methadone, and buprenorphine to treat severe pain. Adjunctive medications, such as gabapentin, pregabalin, tricyclic anti-depressants (TCAs), and serotonin norepinephrine reuptake inhibitors (SNRIs), can be added at any step of the ladder.[33]

When pharmacologic interventions for pain management in CKD/ESRD are being implemented, it is best to identify the level of current renal function. Moreover, special emphasis should be placed when choosing pharmacologic therapies to prevent further deterioration of renal function and protection of existing renal function in patients with moderate to severe impairment. Therefore, drug adjustments may be required for CKD/ESRD. Two methods of dosing regimen adjustment have been recommended: (1) extending the time between doses while maintaining the same dose size (reducing the number of daily doses) or (2) to reduce the size of the individual prescribed dose at the same dosing interval.[16] Sometimes, a combination method can be needed when both these methods (interval extension and dose reduction) are used. The interval extension method is generally not indicated for drugs with a short half-life because of the risk of a prolonged period with a subtherapeutic drug concentration. However, it is recommended for drugs with a relatively long half-life.[16]

Non-opioid Medications

Acetaminophen is the most commonly used non-opioid analgesic for ESRD.[34] Notably, the National Kidney Foundation promotes acetaminophen as the non-narcotic analgesic of choice for mild

to moderate pain in CKD/ESRD.[8] The proposed adjustment in HD patients suggests dosing every 8 h.[35] Clinical studies have shown the effective removal of acetaminophen and its metabolites by HD.[36]

NSAIDs are commonly prescribed for their inflammatory and analgesic properties. However, they are known to have gastrointestinal, cardiovascular, and renal toxicity. Clinical investigations on NSAIDs in patients with CKD/ESRD are typically single-dose studies or trials conducted for short periods and were not designed to evaluate efficacy and safety.[16] Limited information is currently available regarding the use of NSAIDs in patients undergoing HD. Considering the potential for nephrotoxicity, it is strongly recommended to avoid NSAIDs in patients with CKD/ESRD.[16] Despite this, the literature suggests that they continue to be commonly prescribed in this population. In a cohort study of 972 subjects with CKD, 16.9% used NSAIDs every day or several times a week, which increased to 35% among those on HD.[37] In 46.7% of these cases, the CKD/ESRD patients used NSAIDs without being advised to do so by a medical professional and were unaware of the potential side effects of the painkillers, and the remaining were prescribed by physicians or pharmacists. Over 40% of the exposed patients experienced renal function deterioration in this cohort, 37.6% experienced peptic ulcer disease, and 18.2% experienced altered blood pressure control.[37] Thus if NSAID use is considered in patients with kidney disease, a full description of risks and benefits should be discussed with the patient, and ongoing monitoring of renal function throughout treatment should be performed. Topical NSAIDs, such as diclofenac gel, can be effectively used without significant systemic adverse effects.[38]

Anti-convulsants, particularly gabapentinoids, are strongly recommended as first line treatment for the management of neuropathic pain conditions, which are common in CKD/ESRD patients.[39] Gabapentin and pregabalin have been specifically evaluated in patients with CKD/ESRD. Dose adjustment is required in terms of dose reduction and interval extension with these medications. Gabapentin has a favorable pharmacokinetic profile. It is excreted unchanged by the kidneys in urine, and plasma concentrations and toxicity correlate with impaired renal function. Its half-life, 6 to 8 h in healthy subjects, decreases to 4 h after HD and increases to 132 h without HD in ESRD patients.[40] The low protein binding makes gabapentin easy to dialyze (approximately 35%). The recommended dose in HD patients is up to 300 mg daily, with a supplemental 200 to 300 mg dose after each HD session.[41]

Similarly, pregabalin is easily dialyzable because it has a low molecular weight, a low volume of distribution (0.5 L/kg), and is not bound to plasma protein.[42] The maximum recommended dose of pregabalin in ESRD patients is reduced to 25 to 75 mg/day, with mental doses after HD. However, a recent prospective, open-label, single-arm study on pregabalin for neuropathic pain in patients undergoing HD evaluated 45 patients carefully titrated to 150 mg during a 12 week study period.[43] The authors reported a 22.2% withdrawal rate because of side effects (mainly drowsiness and dizziness) without serious drug-related adverse events. Pregabalin has been shown to be effective in reducing pain scores and improving QoL.[43] These medications are associated with an increased risk of falls, cognitive impairment, and altered mental status in a dose-dependent fashion.[44] These effects may be more pronounced in the elderly population.

Alternative neuropathic analgesics such as SNRI and tricyclic anti-depressants (TCA) have been extensively studied and are reported to be efficacious in non-CKD/ESRD populations and are recommended as first or second line treatment in many neuropathic chronic pain conditions. However, data supporting the safety and efficacy of these medications in CKD/ESRD are not available. These medications are not removed by HD, and the anticholinergic and serotonergic effects of these medications may be intensified in patients with ESRD. A recent systematic review concluded that most studies on anti-depressants for depression in ESRD patients involved a small number of subjects and were observational, leading to possible bias. Dose reduction is currently recommended for duloxetine, amitriptyline, venlafaxine, desvenlafaxine, and milnacipran.[45] In general, anti-depressants should be started at lower doses and carefully titrated to the effective dose to reduce the risk of side effects.[46]

Opioid Medications

Opioids are widely used in chronic pain management and historically have been the mainstay of pharmacologic treatment for severe and refractory chronic pain. However, there is no high-quality clinical evidence for their long term use in chronic non-cancer pain, and systematic reviews have only reported a moderate benefit.[47] The Centers for Disease Control and Prevention (CDC) current guidelines recommend a cautious opioid prescription for chronic pain in which non-opioid therapy is indicated as the preferred treatment for chronic pain and opioid use is suggested only when the benefits for pain and function are expected to outweigh the risks.[48] Compared with the general population, patients with CKD and ESRD are likely to be undertreated with opioids because of provider concerns about decreased metabolism and clearance and the increased risk of adverse events.[49] Should opioid use be initiated in CKD/ESRD patients, it is recommended that they be started with the lowest possible dose and using immediate release formulations (instead of extended release).[50] If the pain does not respond with an improvement in pain using a low dose, the pain may not be opioid-responsive. If the pain responds slightly, for either a lower degree or a shorter period than desired, it may be reasonable to increase the dose or frequency. Prescribers should be cautious with opioids at a morphine milligram equivalent daily dose (MME) above 50 mg. Concurrent benzodiazepines and other sedatives should be avoided in line with the current CDC guidelines.

The therapeutic window for opioid medications is narrow, even in a generally healthy population. Individuals with CKD or ESRD have not been included in many trials of opioid use in chronic pain, so the specific analgesic impact of opioids is not known in this population. However, individuals with CKD and ESRD likely experience many known side effects of opioids, including sedation, confusion, and constipation. While the literature on these specific adverse effects is limited in populations with CKD/ESRD, they are well documented in the elderly, which represents a high proportion of individuals with CKD/ESRD. Even low dose opioids are associated with increased morbidity and mortality in the context of ESRD.[51,52]

ESRD and HD lead to additional complications related to the metabolism and dialyzability of opioid medications. Most naturally occurring opioids have active metabolites, which may lead to increased toxicity in patients with CKD/ESRD. For example, morphine and codeine are metabolized in the liver to the active metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), respectively.[33,53] These metabolites are known to accumulate in patients with impaired kidney function,

and their accumulation can lead to potential neurotoxicity and other adverse reactions, such as nausea, vomiting, and respiratory depression. The active metabolite of meperidine, normeperidine, is renally excreted and highly neurotoxic.[33,53] When it accumulates in patients with CKD and ESRD, it places them at a high risk of seizures. Morphine, codeine, and meperidine are generally avoided in patients with decreased kidney function, similar to a few other opioids (Table 47.2).

Semi-synthetic opioids such as hydromorphone, synthetic opioids (e.g. fentanyl and methadone), and the semi-synthetic opioid buprenorphine do not have active metabolites and are reported to have a higher safety profile in patients with CKD and ESRD.[16,50] Although oxycodone is metabolized by the liver into active metabolites that may accumulate in CKD/ESRD, it may be used cautiously in these patients. However, sustained-release formulations should be avoided because of the risk of accumulation and toxicity.[16,50] Buprenorphine has a lower risk profile and can be utilized with either split dosing or a continuous transdermal patch.[54] Tramadol belongs to a class of medications with a dual mode of action, both as an agonist of the μ-opioid receptor and as an SNRI. Since its metabolism depends on an individual's cytochrome P450 profile, its opioid metabolism and resultant potency are highly variable and unpredictable.[55] It is generally considered safe in the general population and in CKD and ESRD in its immediate release formulation.[8,56] However, given the variability in effect, it should be used cautiously, starting with the smallest dose in patients with ESRD. Limited data exist for the safety of extended release tramadol in CKD and ESRD, and as such, its use in this population is not recommended.[8,56]

As in any patient population, when prescribing opioids, providers should educate patients on the risks of opioid overdose and incorporate risk mitigation strategies into the treatment plan. This includes considering a prescription for naloxone, an opioid antagonist, when risk factors for opioid overdose, such as a history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use, are present.[48]

Liver Disease

Prevalence

Liver disease is a major public health problem, accounting for over 700,000 deaths annually.[57] Pain is very common in patients with liver disease, and it is often difficult for practitioners to manage because of underlying medical comorbidities. Pain has been reported in up to 82% of patients with liver cirrhosis and is chronic in over half of the patients with liver it.[58] Despite the high prevalence of pain in this population and its potential for adverse consequences, there is limited research, knowledge, and guidance on the management of pain in liver disease and cirrhosis, with most available literature focusing on pain assessment and treatment in cirrhotic disease.

Assessment of Pain in Liver Disease and Cirrhosis

An evaluation of pain in patients with liver disease or cirrhosis can be accomplished via standard screening assessments, such as numeric or visual analog rating scales. As with the general population, as discussed in detail in the previous section on renal disease, once pain has been identified as being present, the next step is to determine the nature and likely mechanism of the pain, including location, quality, and duration, and perform a physical examination to assess underlying etiology.[58]

TABLE 47.2 Opioid Medications to be Avoided in Chronic Kidney Disease/End Stage Renal Disease

Medication	Pharmacokinetics in CKD and ESRD	Known Observed Toxicities
Morphine	Active metabolite morphine-6-glucuronide (M6G) is renally cleared M6G accumulates in renal insufficiency M6G concentrations are 15 times higher in HD patients than those with normal renal function	Respiratory depression Central nervous system depression Seizures Myoclonus Lethal overdose
Codeine	Hepatic metabolism into active metabolites Reduced clearance of parent drug and metabolites in renal insufficiency Risk for drug accumulation in HD patients	Nausea and vomiting Hypotension Respiratory depression or arrest CNS depression
Hydrocodone	Limited data in renal disease and failure 85% of an oral dose is excreted as parent drug or metabolite in the urine within 24 h Risks of adverse effects are increased with renal insufficiency and drug accumulation	
Tapentadol	Limited data on use in renal insufficiency and failure Undergoes first pass metabolism into inactive metabolites, 99% of which are excreted in the urine AUC of the metabolite is increased 5.5 times in severe renal insufficiency	
Meperidine	Hepatic metabolism into active metabolite normeperidine, which is renally excreted Half-life of normeperidine is increased in renal insufficiency HD has been reported in case of overdose, suggesting the drug can be dialyzed	Mental status changes, seizures
Tramadol (especially Extended Release)	Limited data - Has not been studied in renal disease	Seizures Serotonin syndrome

Special Considerations in Patients With Liver Disease and Cirrhosis

Most patients with liver disease and cirrhosis reporting pain describe abdominal pain as their primary pain area. However, a large proportion of patients also report pain in the lower back, large joints, and diffusely.[59] As non-alcoholic fatty liver disease increases in prevalence, it may overlap with other common non-hepatic painful conditions, such as osteoarthritis, which is a common etiologic factor of obesity. As with renal disease, specific considerations should be noted that are intrinsic and related to the disease process itself. The high prevalence of abdominal pain in patients with liver disease and cirrhosis is likely related to several factors, including liver capsular distension, ascites, peritonitis, and splenomegaly.[58,59] Notably, cirrhosis is a pro-inflammatory state, and the same cytokines associated with cirrhosis are also associated with pain. Fibromyalgia-like syndrome has been found in both hepatitis C virus (HCV) and non-HCV-related liver disease, which may be related to this systemic inflammation.[60]

Pain Management Approach in Patients With Liver Disease

General Principles

The management of pain in patients with liver disease and cirrhosis is complex, and the risk of an adverse event related to pain treatment is high.[61] Similar to the treatment of pain in any patient, the pain management plan for patients with liver disease or cirrhosis should focus on improving physical and other functional outcomes. The treatment plan should be individualized with consideration of physical, behavioral, pharmacologic, and procedural approaches and is best accomplished with a multi-disciplinary approach, including behavioral health, palliative care, or chronic pain specialists.[61]

Much of the apprehension and barriers to treatment of pain in liver disease and cirrhosis stems from the risk of encephalopathy, bleeding, hepatorenal syndrome, and the association of many analgesic agents, such as acetaminophen and NSAIDs, with additional drug-induced liver injury. Furthermore, there is also an increased risk of adverse drug reactions, including over-sedation or overdose, constipation, and altered drug metabolism and pharmacokinetics in patients with chronic liver disease. As such, to provide effective analgesia and reduce the risk of adverse events or side effects, it is important to consider how severe liver disease can alter the metabolism and action of analgesic agents. There is a considerable paucity of literature to guide physicians in this area, given the public health impact of liver disease.[62,63]

Drug Metabolism in Liver Disease and Cirrhosis

The liver plays an important role in the distribution and elimination of most drugs, including analgesic therapies. Generally, drug metabolism in the liver occurs through 1) conjugation; 2) oxidation, reduction, or hydrolysis reactions via hepatic cytochrome P450 (CYP) enzymes; and 3) biliary excretion and elimination.[57] The efficiency of removal of the analgesic drug relies on a variety of factors, including blood flow, plasma protein binding, and intrinsic activity of CYP enzymes. Liver disease and cirrhosis affect all these processes and can alter the metabolism and elimination of many drugs. Generally speaking, the more advanced the liver disease, the greater the impairment of these processes. Unlike renal disease, there is no accurate measure of liver disease severity that can be used to guide dose adjustment. It is recommended that in patients with more advanced or decompensated liver disease, who are at greater risk of adverse drug reactions, close monitoring is employed, and gradual dose uptitration be utilized while balancing side effects such as sedation.[61]

Nonpharmacologic Pain Management in Patients With Liver Disease or Cirrhosis

As described previously, in patients with renal disease, a biopsychosocial approach to pain includes nonpharmacologic options such as simple heat and cold therapy, weight loss, physical therapy, massage therapy, acupuncture/acupressure, CBT, and meditation. Unfortunately, there are no data regarding the efficacy or use of these modalities in patients with liver disease or cirrhosis.

Pharmacologic Pain Management in Patients With Liver Disease or Cirrhosis

As discussed previously, the pharmacologic approach to pain management is particularly challenging in patients with liver disease and cirrhosis because of altered and often unpredictable drug metabolism.

Non-opioid Medications

Although commonly used by the general public for analgesia, acetaminophen is often avoided in patients with liver disease because of its well-described and potentially fatal hepatotoxicity at higher doses. However, although limited data exist regarding the use of chronic daily acetaminophen in liver disease, it has been reported that a reduced dose of 2 g/day is generally considered safe in patients with cirrhosis.[61–63] This was a double-blind study in which 20 patients with chronic liver disease (of undocumented severity) were treated with acetaminophen (4 g/day) or placebo for 13 days followed by crossover to the alternative treatment for 13 days with no resultant significant changes in liver function laboratory tests.[64] As such, low dose acetaminophen (≤2 gm/day) has been recommended as a first line analgesic for patients with cirrhosis.[58]

Given concerns about hepatic damage with acetaminophen use, patients with liver disease and cirrhosis often take or are prescribed NSAIDs. NSAIDs are likely to be more dangerous in this population.[58] NSAIDs are primarily metabolized by CYP enzymes and are heavily protein-bound. As such, patients with liver disease and cirrhosis are at a much higher risk of renal dysfunction and bleeding complications when using NSAIDs. One case-control study reported an association between NSAID use and an increase in variceal bleeding.[65] Given these significant risks, NSAIDs have been reported as contraindicated in patients with cirrhosis and advanced liver disease.[58]

Non-opioid adjuvant analgesic agents are occasionally required for neuropathic pain from peripheral neuropathy secondary to comorbid diabetes, alcohol use, or HCV-associated cryoglobulinemia.[66] As described previously, gabapentin and pregabalin play a prominent role in the treatment of neuropathic pain. Gabapentin and pregabalin undergo minimal hepatic metabolism with unchanged drug excretion from the kidney.[67] Gabapentin has no significant effects on hepatotoxicity and has been recommended as a first line agent to treat neuropathic pain with a maximum dose of 3600 mg/day, assuming normal renal function. Pregabalin has rare reports of idiopathic liver injury and, although rare, should thus be considered and used as a second line agent to treat gabapentin.[68] Gabapentin and pregabalin are both reasonable first line medications for the treatment of neuropathic pain. However, they can cause sedation and have the potential to lead to cognitive or

mental status depression. As with many other analgesics, the doses should again be slowly initiated and carefully up-titrated with preferential dosing before bed.

Anti-depressants have also been frequently used with moderate success in the treatment of chronic pain, especially neuropathic pain. Tricyclic anti-depressants (TCAs) are commonly used for the treatment of neuropathic pain, are metabolized by CYP enzymes, and rely on renal elimination. As a result, drug accumulation can be observed in progressive liver disease. However, its use in patients with liver disease and cirrhosis has been reported to be relatively safe at low doses and in the short term.[69] Starting TCA therapy at the lowest dose with slow titration is suggested with co-administration of laxatives to prevent constipation-induced encephalopathy.[61]

SNRIs, including venlafaxine and duloxetine, have also been used in the treatment of neuropathic pain but have been reported to not be good options for patients with severe liver disease or cirrhosis. Duloxetine carries a manufacturer warning of hepatotoxicity, given its implication in numerous cases of drug-induced liver injury, and is not recommended in patients with chronic liver disease.[70] Concerning venlafaxine, significant dose reduction is recommended, which relies heavily on hepatic CYP.[71] Selective serotonin reuptake inhibitors (SSRIs) have generally not been shown to be recommended for the treatment of neuropathic pain in the general population as they have a lower efficacy than TCAs. However, given the risks outlined previously for TCAs and SNRIs, SSRIs could be considered, although more work is needed to determine the effectiveness of SSRIs for chronic pain in this population.

Opioid Medications

Opioid pharmacotherapy needs to be approached with caution in patients with liver disease or cirrhosis, as they are known to cause sedation, constipation, and encephalopathy. Opioid medications are primarily metabolized via CYP450 (CYP2D6 and CYP3A4) and glucuronidation, and both are affected by liver disease.[61,72] Liver disease and cirrhosis are risk factors for prescription opioid toxicity and/or overdose, and it has been reported that opioid use is associated with poor liver transplant outcomes.[73,74] Furthermore, a history of substance abuse is common in patients with liver disease and cirrhosis. As such, prescription opioids can lead to dependence, addiction, and use disorder, particularly among those with a history of addiction; in general, opioids should not be administered as first line analgesic therapy to the extent possible in this population. The decision making process for the use of opioids for the treatment of chronic pain is difficult even in the general population and should only be employed when all non-pharmacologic and non-opioid treatment options have been exhausted. The potential gain in patient function and quality of life is felt to outweigh the significant risks of long term opioids.

To date, no "safe" prescribing limits of opioid medications have been established in the context of liver disease and cirrhosis. However, they are likely much lower than those of the general population. Total daily doses of >50 MME per day have been shown to lead to an increased overdose risk in the general population.[75] However, pre-liver transplant opioid doses as low as 10 MME per day were shown to be associated with significant increases in post-transplant mortality in one study.[74] Extended or sustained-release opioids should be avoided because of the risk of a toxic drug or metabolite accumulation in liver disease or cirrhosis. The combination of opioid-acetaminophen pills should be avoided in patients with cirrhosis because of the potential for additional liver toxicity because of acetaminophen. The metabolism and data regarding the different opioid types are outlined in Table 47.3, based on recent systematic and narrative reviews on opioid use in liver disease.[57,58,61,76] It is highly recommended to ensure that constipation is mitigated through the use of lactulose or other laxatives, as hepatic encephalopathy can occur.[62]

Diabetes

Diabetes is a metabolic disorder that results in impaired glucose tolerance because of deficiency or absence of insulin. According to the American Diabetes Association, approximately 34 million Americans live with type 1 or type 2 diabetes, which accounts for more than 10% of the United States population. It is worth noting that in pain medicine, we will be treating many patients with diabetes for ailments related to and unrelated to diabetes. Chronic pain is the most common complication of diabetes.[77] This pain syndrome is discussed in more detail in Chapter 34.

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is the most common type of pain syndrome related to diabetes. Like other peripheral neuropathies, it presents as a length-dependent neuropathy in the typical stocking and glove distribution. As many as 26% of patients with diabetes develop diabetic peripheral neuropathy.[78] Glycemic control is seen as an important preventative measure and may help slow the progression of neuropathy after it has been presented.

Painful diabetic peripheral neuropathy can have severe effects on a patient's wellbeing. Patients often experience mood disturbances, decreased quality of sleep, increased levels of pain, and reduced quality of life.[79]

Painful diabetic peripheral neuropathy (PDPN) is a difficult to treat condition, and many of the medications used to treat this condition are only mildly helpful, leaving the patient in continued distress despite treatment. First line therapies include medications such as tricyclic anti-depressants, serotonin-noradrenaline reuptake inhibitors, and anti-convulsants. Opioids are often reserved for second or third line therapies because of their limited effect on neuropathic pain and the risk of side effects.

Other Painful Conditions Related to Diabetes

While diabetic peripheral neuropathy is the most common and well known painful condition related to diabetes, there are several other diagnoses that the pain medicine practitioner should be familiar with as approximately 50% of people with diabetes will experience a clinically significant neuropathy.[80] Painful neuropathies include mononeuropathy, cranial neuropathy, and plexus neuropathy.

Mononeuropathy: This is characterized by pain and motor dysfunction in the distribution of a single nerve. This can be because of ischemic damage and compressive lesions.[81] The most common nerves affected are the oculomotor and median nerves.

Cranial neuropathy: The most common cranial neuropathy in diabetic patients is oculomotor neuropathy and typically presents as a third nerve palsy with pupillary sparing.[82]

Radiculopathy: Patients with diabetes can have radiculopathy without degenerative spine changes or disc herniation.[81] This is important to avoid unnecessary decompression surgery, as diabetes is a cause of non-compressive radiculopathy.

TABLE 47.3 Opioids Medications in Liver Disease

Medication	Metabolism	Recommendation
Oxycodone	Metabolized into α and β oxycodone metabolites by CYP3A4 and CYP2D6 In advanced liver disease, plasma concentration is increased up to 40%, and the half-life of the IR formulation is increased from 6.4 to 24.6 h (average 14 h, normal half-life is 3.5 h) Bioavailability is dramatically increased	The initial dose should be reduced to 30%-50% of the usual starting dose The interval between doses should be lengthened
Codeine	Prodrug, which is converted to morphine by CYP2D6 Limited metabolism may lead to poor analgesic effects Morphinemia because of delayed clearance of metabolite may lead to significant respiratory depression and overdose	Not recommended for use in liver disease or cirrhosis
Meperidine	Converted to normeperidine through hydrolysis by CYP3A4 and CYP2B6 Clearance is reduced, and half-life prolonged Accumulation can lead to respiratory depression, seizures, CNS depression, and encephalopathy	Not recommended for use in liver disease or cirrhosis
Methadone	Metabolized by CYP3A4 and CYP12A Clearance is reduced in liver disease, and the compound has a long half-life Does not produce toxic metabolites High affinity for binding to proteins	In mild hepatic disease, may use with caution and start low/go slow as data has shown no change in dose is required with mild impairment In patients with moderate liver disease with or without hypoalbuminemia, caution is advised with dose reduction and less frequent dosing Contraindicated in severe liver disease
Tramadol	Metabolized by CYP3A4 and CYP2D6 Metabolism to active metabolites may be reduced, thus decreasing analgesic efficacy	More research needed, alternative therapies are recommended Caution advised if used in patients with a seizure disorder or concomitant SNRI, TCA, or SSRI use
Morphine	Undergoes significant first pass metabolism via glucuronidation Liver disease decreases glucuronidation and therefore leads to increased bioavailability, decreased clearance, and a prolonged half-life	Caution advised Decreased dosing with an increased time between dosing and slow titration
Hydromorphone	Does not require metabolism to an active metabolite Undergoes significant first pass metabolism via glucuronidation, which is decreased in liver disease Leads to higher bioavailability Metabolites not known to be neurotoxic	Decrease usual start dose by 50%-75%, titrate slowly
Fentanyl	Metabolized by CYP3A4 Clearance can be decreased in liver disease with decreased hepatic blood flow Heavily protein-bound Pharmacokinetics of single intravenous dose similar to healthy controls in well-compensated liver disease with preserved hepatic blood flow These findings cannot be extrapolated to transdermal fentanyl preparations	Transdermal preparation not adequately studied can assume decreased absorption, metabolism, and clearance. Should be avoided in patients with severe hepatic impairment
Hydrocodone	Pre-drug that is metabolized into hydromorphone and oxymorphone by CYP2D6 Half-life is increased in liver disease	Decrease initial dose by at least 50% and titrate slowly, with a possible increase in time between dosing

Mononeuritis multiplex affects multiple nerve trunks that cause dysesthesia and paresthesia, likely related to ischemia.[83]

Insulin neuritis/treatment-induced neuropathy. Secondary to aggressive control of glucose levels in a previously hyperglycemic patient, insulin neuritis presents as a symmetric distal neuropathy combined with autonomic dysfunction and acute pain after rapid glucose regulation, such as initiation of insulin therapy.[84] The condition is often reversible, but the pain can be persistent and is often difficult to treat and refractory to typical neuropathic pain medication therapy.

Medication Management

Tricyclic Anti-depressants

Originally designed for mood disorders, it is common to utilize this class of medications for neuropathic pain within the pain medicine community. Commonly used medications in this class include nortriptyline, amitriptyline, and desipramine. Dosing is initiated at a low nightly dose, such as 10 to 25 mg per night. The dose was then increased every five to seven days until a goal dose was attained, pain relief was achieved, or adverse effects were encountered. Compared to the SSRI and SNRI type of medications, pain

relief with TCAs is similarly delayed in onset.[85] Unfortunately, adverse effects are not uncommon and include somnolence, dizziness, urinary retention, and increased risk of falls.[86] Extra caution should be exercised in patients with urinary retention, baseline increased fall risk, and underlying cardiac disease. Typically, the first medication trialed in this category is amitriptyline, with nortriptyline as a secondary alternative if amitriptyline is ineffective or poorly tolerated. Desipramine is often not utilized because of the increased risk of adverse effects compared to amitriptyline and nortriptyline.

Serotonin-Norepinephrine Reuptake Inhibitors/Selective Serotonin Reuptake Inhibitors

Serotonin agonists are another category of medications that are frequently used for the treatment of PDPN. One of the most commonly used agent is duloxetine.

This is initiated at 30 mg daily for two weeks and then increased to 60 mg daily for most patients. This medication can take up to 12 weeks to take full effect, and studies have shown that while the 60 mg and 120 mg daily doses are successful in treating PDN, the 20 mg daily dose is not.[87] Patients must be counseled about this delayed onset to encourage compliance. Common adverse effects include nausea, dry mouth, sweating, and constipation. Many of these can be abated by starting the medication at a lower dose to develop tolerance to serotonin effects. SNRIs may help treat pain when there is also a mood disorder.

Anti-convulsants

To date, the most common anti-convulsants utilized for neuropathic pain are gabapentin and pregabalin, and they have both been shown to be effective for PDPN.[88,89] Gabapentinoids, which include both gabapentin and pregabalin, act by inhibiting calcium currents by binding with the alpha two δ subunit of voltage-gated calcium channels.[90] The benefit of gabapentin is that it is inexpensive, typically well tolerated, and has proven efficacy. This medication was started at a low dose and titrated to effect as tolerated. Many times for neuropathic pain, patients will need to titrate up to 2700 mg/day or higher. While some patients will experience substantial pain relief with pregabalin, most will have moderate pain relief, and many will have no relief at all.[91]

Opioids

Opioids are not the first line therapeutic agents for PDPN. However, some are more successful in treating neuropathic pain than others. Medications that combine activity at the NMDA receptor and the opioid receptor may have a higher likelihood of treating neuropathic pain than pure mu agonists. Examples of these opioids include tramadol and methadone. Low dose naltrexone, a reversible competitive antagonist of μ-opioid and κ-opioid receptors, is also gaining popularity. When used at low doses of 1 to 5 mg daily, naltrexone acts as a glial modulator with a neuroprotective effect via inhibition of microglial activation.[92]

Topical Agents

Often, topical agents are used for PDPN with mixed results. The efficacy of 0.075% capsaicin lotion was similar to that of placebo in one study, but it was well tolerated.[93] In another study, a single 30 min application of the capsaicin 8% dermal patch provided 12 weeks of pain relief and improved quality of sleep.[94] In this scenario, patients can undergo repeat treatment with the capsaicin 8% dermal patch as needed.

In summary, many medications are options for the treatment of PDPN and other diabetes-related painful conditions. They must all be tailored to each patient's specific needs and risk factors to create a personalized approach that maximizes the response and minimizes the side effect profile.[95] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends amitriptyline, duloxetine, pregabalin, and gabapentin as the initial treatment for PDPN. If this is not effective, combination therapy will be the next step.[96] If medication management is ineffective, other strategies for pain control should be considered.

Botulinum Toxin

Botulinum toxin A has been shown to significantly improve PDPN.[97] Botulinum toxin A has long been known to decrease neuropathic pain by preventing the fusion of synaptic vesicles with the cell membrane, thus halting the release of neurotransmitters.[98] With peripheral neuropathy, BTa is injected in the area of pain, utilizing a grid-like pattern. Pain relief typically presents within one to two weeks of injection and can last for up to 12 weeks.

Scrambler Therapy

When PDPN fails to respond to conventional first and second line treatments, scrambler therapy may be an option for otherwise intractable neuropathy.[99] Scrambler therapy is similar to TENS in that the electrodes are placed on the skin. However, in scrambler therapy, electrodes are placed in the non-painful area. During treatment, the patient perceives non-painful sensations, such as itching or pressure, in the previously painful area. The proposed analgesic mechanism of scrambler therapy includes the electrodes sending non-painful impulses to the peripheral receptors, with the A δ and C fibers relaying the stimuli to the CNS. Scrambler therapy has been shown to be effective in some neuropathic pain syndromes.[99]

Integrative therapies, including mindfulness and progressive relaxation, have been shown to reduce chronic pain in women with diabetes.[77] In addition, Rozworska et al. demonstrated that participation in mindfulness-based stress reduction leads to an improvement in pain related outcomes.[100] Acupuncture has also been shown to improve symptoms of PDPN symptoms.[101] Exercise has also been considered to reduce pain interference in this patient population without actually decreasing the pain score itself.[102]

Regenerative Medicine

Growing evidence suggests that increased inflammatory factors, combined with a deficiency of angiogenic factors, contribute to the underlying pathology of PDPN. Studies have shown that bone marrow-derived stem cells (BMCs) may be a promising strategy for tissue repair.[103] Known to inhibit inflammation and promote angiogenesis, BMCs may be a novel therapeutic option for patients with PDPN.

Spinal Cord Stimulation

SCS has been shown to reduce pain experienced by PDPN.[104] As peripheral blood flow is a fundamental part of the pathophysiology of PDPN, peripheral vasodilation, and improved blood flow are potentially beneficial secondary effects of SCS is peripheral vasodilation and improved blood flow.[105]

Surgery

Surgery can be utilized for the treatment of superimposed peripheral nerve entrapment syndrome in patients with diabetic peripheral

neuropathy, sometimes with pain relief and restored sensation. One study evaluated the effects of microsurgical decompression of multiple entrapped peripheral nerves in patients with refractory PDPN of the lower limbs. Bodily pain was significantly reduced two weeks after the procedure.[106]

Conclusion

For pain medicine practitioners treating patients with diabetes, it is important to consider their overall health when initiating therapy for painful conditions. Opioid medications may lead to increased nausea in patients with diabetes-related gastroparesis. Steroid injections may also lead to hyperglycemia. The dosing of medications may need to be adjusted in the setting of renal failure or dialysis. With comprehensive analysis and attention to detail, we can treat these patients safely and offer them the full spectrum of multi-disciplinary pain management in hopes of restoring function and improving their quality of life.

Pain Management in Older Adults

Background

An estimated 51 million Americans are over the age of 65 years, which is about 16% of the American population (United States Census Bureau, population projections). Up to 65% of people over the age of 65 years experience pain, and up to 30% have chronic pain (painconsortium.nih.gov). Older adults are more likely to experience pain than younger individuals.[107] Diagnosing and treating pain in older individuals can be difficult because of differences in patient reporting, communication barriers, and underlying comorbidities. The most common chronic pain conditions are arthritis, back or neck pain, and joint pain, which are present in 48%, 45%, and 41% of older Americans, respectively.[108,109] Up to 50% of patients in nursing homes use analgesic therapy for the treatment of pain, and some sources report that up to 80% of nursing home patients suffer from pain.[110] Hence, this is a significant problem in the aging population. Pain physicians need to have a thorough understanding of the mechanisms underlying pain in this population and the physiologic changes that affect the efficacy and side effect profile of our treatment options. For many reasons, both provider-related and patient-related pain is significantly under treatment in this patient population.[111] The importance of pain management in this population cannot be overstated. Poor pain control can lead to a lack of socialization, poor sleep, depression, increased healthcare costs, and reduced quality of life.[112,113]

Evaluation: Assessment and Physical Examination

Assessment

Understand that the older patient population may not present in the same way as younger individuals, and failure to recognize pain leads to an inability to treat pain. Older adults often present with multiple painful conditions. Therefore there is a need for comprehensive evaluation.[114] In addition, multiple comorbidities may make it difficult to determine the underlying cause of pain. A careful history, thorough physical examination, and diagnostic studies, including imaging and nerve conduction studies, can all help identify the source of pain. Prior to obtaining the patient's history, the ability of the patient to report pain should be assessed. If the patient cannot provide history, the provider should supplement the history with other proxies for self-reporting. The history should detail the onset of pain, the location of the pain, the character of the pain, and any recent changes in the way the pain is present. Be mindful to use words other than pain, as patients in this cohort may identify with words like "ache" or "discomfort" more than pain. Methods to understand baseline pain and determine the response to pain-directed treatments are similar to those of younger patients. However, self-reported pain relief may need to be supplemented by behavioral observation, data from caregivers and family members, and pain behavior tools. The lack of appropriate assessment tools can be a barrier to appropriate pain assessment.[115] Our most common pain assessment tool, the VAS, does not work well for older patients with pain.[116] A variety of other pain assessment tools are used to include the faces pain scale, NRS, verbal descriptor scale, pain thermometer, pictorial pain scales.[112,116] In addition, cultural beliefs about the importance of stoicism in this age group may lead to underreporting by the patient.[117] Therefore rewording questions are useful. A patient may report low levels of pain, but when questioned about discomfort or aches, significant findings will be reported. It is helpful to take note of nonverbal cues during history and physical examination to assess for pain that is underreported or not effectively communicated. The checklist of nonverbal pain indicators (CNPI) and the pain assessment in advanced dementia are two behavioral observation tools available.[118] These tools are discussed in Chapters 43 (geriatric pain management), 79 (pain evaluation in patients with limited ability to communicate), and 84 (outcome domains in chronic and acute pain). In addition to pain severity, it is crucial to understand the level of interference pain that may affect individuals' function and quality of life. The level of interference can be evaluated by asking about fatigue, disturbed sleep, activity level, mental health, and quality of life.[119]

Physical Examination

Physical examination should be comprehensive, focusing mostly on the musculoskeletal and neurologic systems. When assessing neurologic function, it is important to evaluate the strength, response to light touch and pinprick, and sensation. When assessing musculoskeletal function, examining joint swelling, range of motion, tenderness to palpation, muscular pain, and straight leg raise are all useful.[112] Deconditioning, reduced flexibility, and reduced muscle mass were observed. In addition, age-related loss of tendon reflexes is important to note, and attention should be paid to asymmetric changes instead of a global decrease in reflexes.[120]

Evaluation of Common Painful Syndromes

Osteoarthritis

Osteoarthritis (OA) is a very common condition in geriatric patients and can significantly affect the quality of life and ability to be active. Symptoms of OA include stiffness, pain, decreased range of motion, and disability. Age is an independent risk factor for OA, along with obesity, metabolic disease, gender, genetics, and ethnicity.[121]

Neck Pain

Neck pain is common in the geriatric population and is often multifactorial with pain generators, including osteoarthritis, disc degeneration, myofascial pain, cervical spondylosis, and trauma.[122] Neck pain is the fourth leading cause of disability in adults.[123] Available imaging includes plain film (X-ray), computed tomography (CT), magnetic resonance imaging (MRI), and CT myelography.[124] The differential diagnosis and imaging workup of neck pain was determined based on relevant pieces of the patient's history and physical examination. Common indications for cervical imaging include trauma, neurologic deficits, myelopathy or "red flag symptoms," radiculopathy, and persistence of symptoms.[125]

Back Pain

Chronic low back pain is exceedingly common in the elderly population, with up to 25% of those 65 years and older with chronic low back pain.[126] Chronic low back pain is currently the most common cause of disability worldwide.[127] Common causes of low back pain include osteoarthritis, facet joint arthropathy, myofascial pain, lumbar spondylosis, lumbar stenosis, and vertebral compression fractures. Less common causes include infection and tumors. Available imaging includes plain film (X-ray), CT, MRI, and CT myelography. The differential diagnosis and imaging workup of low back pain are determined based on relevant pieces of the patient's history and physical examination. Common indications for lumbar imaging include trauma, neurologic deficits, myelopathy or "red flag symptoms," radiculopathy, and persistence of symptoms.

Medication Considerations for Use in Older Adults

One of the most concerning aspects of pain management in older adults is concerns about the adverse effects of medication therapy. This is a valid concern and may also lead to the treatment of pain in this population. Rather than avoiding medication usage in elderly patients, the pain physician should focus on having a detailed understanding of the differences in dosing and adverse effects in this population to create a sense of security in treating pain and efficiency in recognizing potential adverse effects.

Renal: Avoid medications that can affect renal function, as this is already reduced in elderly patients. In addition, underlying renal issues need to be considered when determining the appropriate dosage to avoid the buildup of toxic metabolites. While NSAIDs are effective agents for inflammatory processes, they are associated with renal toxicity, and severe side effects from NSAIDs are more common among elderly patients.[128]

Hepatic metabolism: Secondary to decreased liver mass and decreased liver perfusion, the first pass effect on medications that are highly cleared by the liver may have increased bioavailability.[129] Dosing decreases should be considered for medications that undergo p450 dependent metabolism.

Pharmacokinetic and pharmacodynamic changes: With advanced age, we know that a reduction in renal and hepatic clearance occurs. In addition, there is an increased volume of distribution of lipid-soluble drugs that can lead to a prolonged elimination half-life.[130] Pharmacodynamic changes lead to increased sensitivity to several classes of medications.[130]

Conclusion

In summary, the evaluation and management of elderly patients requires a thorough understanding of how to assess pain in this population, various pain scales to compensate for possible changes in cognition, the most common pain syndromes, and the management of medications in a population that may have pharmacodynamic and pharmacokinetic differences related to aging. Pain should not be undertreated because of barriers in communication, difficulty in physical examination, or a bias that pain is just a part of getting older. With proper care, many elderly patients can have a higher quality of life with minimal interference from their daily activities because of chronic pain.

Summary and Conclusions

When treating patients with chronic pain, it is important to consider their overall health and potential complications when initiating medications and considering interventions. Many of these patients with renal or liver disease, diabetes, and the elderly are often excellent candidates for multi-disciplinary pain management, including psychology/behavioral health services, functional restoration programs, physical therapy, occupational therapy, and advanced interventional procedures to include neuromodulation. Treatment requires a thorough understanding of the unique characteristics of these patient populations, including altered pharmacokinetics, metabolism, and clearance. Understanding that history and physical evaluation may require different assessments than patients without these chronic conditions or non-elderly patients. Pain medicine providers should be familiar with the most common pain syndromes in these populations and how to treat them. In addition, it is of paramount importance to remember that pain is often undertreated in these patient populations and that with proper care, patients can have increased function and improved quality of life.

Key Points

- Common medical comorbidities that can be encountered in chronic pain conditions are kidney disease, liver disease, diabetes, and the care of elderly patients.
- Pain is one of the most common symptoms of CKD, ESRD, and liver disease.
- The pain experienced by patients with kidney and liver disease is often multifactorial and can be because of the underlying organ-related disease process, hemodialysis, or comorbid diseases.
- Many non-pharmacologic and non-opioid pain management strategies have been shown to be helpful for pain in kidney and liver disease patients. However, further research is needed to establish the efficacy of many of the behavioral and complementary therapies specifically for these populations.
- When pharmacologic interventions for pain management in kidney and liver disease patients are being implemented, it is best to identify the level of current kidney and liver function,

and the focus should be on preventing further damage and adjusting the drug dosage as indicated.
- While diabetic peripheral neuropathy is the most common and well known painful condition related to diabetes, there are several other diagnoses that pain medicine practitioners should be familiar with, as approximately 50% of people with diabetes will experience clinically significant neuropathy.
- The most common anti-convulsants utilized for neuropathic pain are gabapentin and pregabalin, both of which have been shown to be effective for PDPN.
- Opioids are not first line therapeutic agents for PDPN.
- Pain is often undertreated in elderly patients.
- Pain should not be undertreated because of barriers in communication, difficulty in physical examination, or a bias that pain is just a part of getting older.
- The older population may have pharmacodynamic and pharmacokinetic differences related to aging, which should be considered when managing medication therapy.

Suggested Readings

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PART 5

Pharmacologic, Psychologic, and Physical Medicine Treatments and Associated Issues

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Major Opioids and Chronic Opioid Therapy

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General Considerations of Opioid Administration

Derivatives from the opium plant have been described as analgesics and used for pain control since 3500 BC. It was not until 1806 that a pure opioid substance was isolated. This substance was called "morphine," named after the Greek god Morpheus.[1] Since then, the opium plant has yielded other byproducts, and synthetic analogs of morphine have been produced for medicinal use. The use of opioid medications in the United States has fluctuated because of various factors, including but not limited to production, availability, governmental regulation, and physician and societal attitudes. Fluctuations have also occurred because of guidelines that have shifted their positions. Over the last 20 years, the prescription pattern of opioids has escalated significantly for several reasons. The increasing trend in prescription writing has been accompanied by a concordant rise in the incidence of diversion and abuse, as well as an increase in the incidence of complications, including overdose and death. Over the past several decades, evidence for a sustained benefit of opioids in alleviating chronic pain has remained weak and inadequate, either with results that are not substantially positive or negative or have poor scientific quality. However, evidence of the risk associated with the use of opioid drugs has been increasingly elucidated in the literature and from public health agencies. This change in which evidence of the efficacy of opioids has not changed, whereas risk has increased, should significantly impact treatment decisions based on a critical analysis of risks and benefits. This chapter aims to review clinically relevant aspects of selected opioids, including side effects and pharmacology, and review the current consensus on rational opioid prescription.

Opioid Receptors

Endogenous opioids, in addition to multiple other endogenous systems, are involved in the modulation of pain perception. Natural endogenous opioids include the endogenous peptides β-endorphins, enkephalins, and dynorphins. Since the discovery of opioid receptors in the central nervous system (CNS) in 1973, the body of literature describing their function and location has grown immensely.[2,3] Opioid receptors play integral roles in the endogenous antinociceptive system and, accordingly, are located throughout the central and peripheral nervous systems. The best-described opioid receptors are labeled μ, κ, and δ and are prominently located in the CNS, particularly in the dorsal horn of the spinal cord,[4] as well as in the dorsal root ganglia and peripheral nerves.[5,6] The three opioid receptors identified, μ, κ, and δ, belong to a superfamily of guanine (G) protein-coupled receptors located at pre-synaptic and post-synaptic sites in the CNS and peripheral tissues.[7]

The μ-opioid receptor modulates input from mechanical, chemical, and thermal stimuli at the supraspinal level. The κ receptor is similar to the μ receptor in that it influences thermal nociception. However, it also modulates chemical visceral pain. The δ receptor influences mechanical and inflammatory pain.[8] An opioid agonist, such as morphine, binds primarily to the μ opioid receptor to produce analgesia, as well as undesired side effects, such as respiratory depression and constipation. In a study using knockout mice that lacked the μ receptor, it was found that they did not respond to morphine with respect to analgesia, respiratory depression, constipation, or physical dependence.[9]

Distribution, Metabolism, and Excretion

The amount of opioids required to produce analgesia has significant interindividual variability. The factors responsible for this variability include opioid receptor individuality and variations in opioid absorption and clearance. Such individual variability requires careful titration of opioids to the desired response. The onset, duration, and intensity of analgesia depend on the delivery of the drug to the target and the length of time that the receptor is occupied. The number of receptors occupied and the length of time that the opioid activates its target receptor depends on the perfusion, plasma concentration, pH, and permeability coefficient of the drug.[10]

The metabolic pathway for each opioid is based on the molecular variables of a specific opioid. Opioids with hydroxyl groups, such as morphine and hydromorphone, undergo hepatic metabolism via uridine diphosphate glucuronosyltransferase (UGT) enzymes. UGT adds a glucuronic acid moiety to form glucuronide metabolites such as hydromorphone 3-glucuronide (H3G), morphine 6-glucuronide (M6G), and morphine 3-glucuronide (M3G)). These metabolites

are excreted through the kidneys. Patients with renal impairment are particularly prone to the deleterious effects of metabolite accumulation.[11]

The cytochrome P-450 (CYP) system contains two polymorphic isoforms that metabolize certain opioids. The first CYP isoform responsible for the biotransformation of codeine, oxycodone, and hydrocodone is 2D6. It is estimated that up to 10% of white individuals lack this enzyme, thus making them "poor metabolizers" of certain opioids and providing another cause for the high interindividual variability seen in patients treated with opioids.[11] The 3A4 isoform of the CYP system is involved in the biotransformation of fentanyl and methadone to their inactive forms.[12] Because other drugs also interact with 3A4 isoenzymes, the metabolism of methadone and fentanyl can be problematically decelerated or accelerated. For example, macrolide antibiotics inhibit the enzyme, which decreases the clearance of methadone and fentanyl, whereas anti-convulsants such as phenytoin induce the activation of this enzyme system and increase the clearance of methadone and fentanyl.[13,14] The excretion of most opioid metabolites occurs via the kidneys, but some of the glucuronide conjugates are excreted in bile, and methadone is excreted primarily in feces.[11]

The study of pharmacogenomic polymorphisms is important in understanding the interindividual variability in analgesic effects [the reader is directed to Chapter 13 on pharmacogenetics]. Opioid related therapies have a multiplicity of genetic factors that influence the metabolism and clearance of specified opioids. In the future, the use of regulator-approved pharmacogenomic assays may be advantageous for identifying many of these variant alleles. Understanding pharmacogenomic polymorphisms will most likely play a role in everyday clinical decision making to manage acute and chronic pain. As for safety and patient care benefit from detailed knowledge of specified polymorphisms, this science will most likely be incorporated into the standard of care for physicians.[15]

Administration

Multiple routes of administration are among the many clinically useful characteristics of opioids. Administration can range from intrathecal, intravenous, or oral to rectal, sublingual, buccal, intranasal, or transdermal. Depending on the clinical situation, one route may be more advantageous than the other. For example, a patient who requires continuous opioid delivery but is unable to take medications orally may benefit from a transdermal delivery system, such as is currently available in a transdermal patch containing fentanyl and, more recently, the Food and Drug Administration (FDA) approved transdermal patch containing buprenorphine, which, in appropriate settings, has potential safety advantages over fentanyl. Fentanyl is also available as a rapid onset transmucosal delivery product. Neuraxial routes of opioid delivery are widely used in perioperative and postoperative care, as well as in terminally ill patients.

The pharmacologic goal of effective opioid therapy for chronic pain is to provide sustained analgesia over regular intervals.[16] This requires consideration of several factors, including knowledge of equianalgesic dosages between opioids and the pharmacologic properties and side effects of specific opioid agents. Pain in opioid tolerant patients is particularly challenging because typical dosages for opioid-naïve patients do not apply, and exact opioid requirements may require careful titration.

Whether fixed dosing is better than as-needed (PRN) dosing is controversial, with each method having advantages in specific patient settings. With fixed dosing, there is consistent opioid delivery, which can theoretically reach steady state levels.[17] Presumably, this avoids the peak-and-trough effect that can be associated with on-demand dosing and may prevent delays in delivery that can occur with on-demand schedules. One problem for opioid-naïve patients who receive fixed doses of opioids with longer half-lives is that they may experience excessive side effects or toxicity because of the difficulty in predicting the exact opioid requirement and potential accumulation. For example, morphine may take less than 24 h to reach steady state levels, whereas methadone can take up to one week. When there is a need to assess a patient's analgesia threshold, PRN dosing of an opioid with a short half-life may be used, or conservative fixed dosing of opioids with a short half-life, supplemented by PRN "rescue" dosing, may be used.

Analgesic therapy with long-acting opioids (LAOs) offers convenient dose intervals to attain safe, effective, and steady state levels. Several controlled-release opioids are available, including morphine (MS Contin, Oramorph SR, Kadian), hydrocodone (Hysingla), oxycodone (OxyContin, Xtampza), fentanyl (Duragesic patch), hydromorphone (Exalgo), tapentadol (Nucynta ER), and oxymorphone. Methadone may be used as a relatively LAO (longer effect than short-acting opioids [SAO] but shorter than most LAOs), but it poses specific issues and concerns for clinicians that are distinct from those of other opioids (see later discussion). Methadone has a faster onset and longer analgesic effect than many other SAOs and may be ideal in some situations. However, other properties and adverse effects may limit their use. Methadone is not specifically formulated for a sustained release like other LAOs, which essentially release an SAO throughout the drug's passage through the gastrointestinal (GI) tract. Methadone has an intrinsically longer plasma half-life than other typical opioids, such as hydromorphone (Dilaudid) and morphine, and can therefore be advantageous in patients with GI motility issues such as short gut syndrome.

Although sustained- and immediate-release opioid preparations have made the oral route a practical option, some patients cannot tolerate oral delivery.[18] In such cases, transdermal, buccal, rectal, intravenous, or subcutaneous infusions are often a practical alternative option. With infusion, the first-pass effect is eliminated, potentially offering some advantages. There may be a faster onset of analgesia with less complicated access when compared with the oral route. Compared with the intramuscular route, the administration is often less painful and may be safer in patients with bleeding disorders or reduced muscle mass.

Adverse Effects

The most commonly encountered side effects associated with opioids include constipation, nausea, vomiting, sedation, urinary retention, pruritus, and hypogonadism. Although respiratory depression may not be as common, its potentially devastating effects make it a heightened concern. Any of these side effects can significantly limit therapy, but the resolution of most adverse effects may occur shortly after the initiation of opioids. However, constipation is a major exception because it does not resolve with the prolonged use of opioids. Particular attention should be given to older adults and patients with hepatic or renal insufficiency. Tolerance (drug effect wears off

over time or higher dosage is needed to achieve the same effect) and physical dependency (sudden discontinuation produces withdrawal effects) are also commonly associated with opioid therapy. These are pharmacologic properties related to opioids that are frequently misinterpreted as indicators of addiction. Addiction is also a potential risk associated with opioid use (see later discussion). Physicians should anticipate any or all of these adverse effects, remain vigilant throughout therapy, and monitor patients closely, particularly when initiating therapy and escalating opioid doses.

Constipation

The most common side effect of opioid administration is constipation; unfortunately, tolerance to it does not generally develop. Constipation can cause significant discomfort, nausea, and emesis. One of the underlying mechanisms of opioid-induced constipation is thought to be decreased gastric motility because of opioid binding to highly concentrated μ-opioid receptors located in the antrum of the stomach and the proximal part of the small bowel.[19,20] There is limited evidence that certain opioids at equianalgesic doses produce more or less constipation than others. Because the transdermal route bypasses initial exposure to the GI tract, transdermal fentanyl has been postulated to produce less constipation than orally administered opioids.[21–23] However, current data are not convincing and transdermal opioids are well-known to result in significant constipation, such as that associated with oral opioids, which may require aggressive management.

When initiating any opioid, it is important to prescribe medications to maintain regular bowel motility concomitantly. Treatment of opioid-induced constipation should include an active laxative such as senna, lactulose, or bisacodyl or osmotic agents such as polyethylene glycol; passive agents such as stool softeners or fiber-based bulking agents may be ineffective because they rely on triggering gastric motility, which in the case of opioids may be inhibited. Alternatively, the use of an adjunctive agent with a side effect profile that includes diarrhea, such as misoprostol, can coexist well with constipation. However, misoprostol should be used with caution in women of childbearing age because it can initiate uterine contractions and miscarriage.[24,25]

Peripheral opioid receptor antagonists have also been shown to be effective in refractory cases of opioid-induced constipation. Methylnaltrexone, a quaternary derivative of naltrexone, contains a permanently charged tetravalent nitrogen atom and cannot cross the blood-brain barrier.[26,27] Methylnaltrexone is an antagonist of the μ receptor. It blocks the peripheral actions of opioids while sparing their central analgesic effects and reverses the slowing of bowel motility, which often occurs with opioid related therapy. Methylnaltrexone was approved by the United States FDA in 2008 as an indication of opioid-induced constipation. Alvimopan, which was also approved in 2008 by the FDA, functions as a peripherally acting μ-opioid antagonist with limited ability to cross the blood-brain barrier. Alvimopan, naloxegol, and naldemedine are opioid receptor antagonists that can treat constipation without, in most cases, affecting analgesia or precipitating withdrawal. The primary indication for this medication is the avoidance of postoperative ileus following partial large or small bowel resection with primary anastomosis.[26,27] In addition to the opioid receptor antagonists, lubiprostone is approved by the FDA for the treatment of opioid-induced constipation. However, these options are currently proprietary and costly and are usually reserved specifically for refractory opioid-induced constipation.

Nausea and Emesis

Nausea and vomiting are frequently seen in patients who are treated with opioids, but it is usually a transient side effect that often lasts only two to three days. The underlying mechanisms of nausea and vomiting appear to be related to several causative factors. One is the activation of receptors in the brainstem, which produces afferent input to the medullary chemoreceptor trigger zone, which is responsible for afferent input to the emetic center of the brain. These areas are dense in neurotransmitter receptors, which correspond to the antiemetic agents used clinically. A potential cause of nausea is the stimulation of receptors in the vestibular apparatus.[28,29] Another underappreciated cause of opioid related nausea is constipation, which often responds to treatments that increase motility.

In evaluating a patient who reports nausea and vomiting while taking opioids, one should determine important history-related factors involved in the genesis of nausea, such as the time of the last bowel movement, whether it worsens with movement, or whether there is a temporal relationship between opioid ingestion and the onset of nausea. The choice of antiemetic agent depends on the historical aspects of the reported side effects. Patients who experience nausea when they are more ambulatory may be more likely to experience vestibule-related nausea. In such cases, drugs such as meclizine, promethazine, or scopolamine may be useful in relieving this type of induced nausea. Droperidol, prochlorperazine, ondansetron, or hydroxyzine may have greater benefit for nausea that is not associated with movement, a type of nausea thought to be related to chemoreceptor trigger zone-associated activation.[30,31] However, cardiac adverse effects may be reflected on the electrocardiogram in QTc elongation. One should also ensure that reversible metabolic causes, intracranial pathology, or other factors such as medications are not the origin of nausea or emesis before it is attributed solely to opioids.

Several approaches can be used to treat opioid-induced nausea and vomiting. An antiemetic may be added, often choosing an agent that offers secondary benefits such as promotility, sedative, antipruritic, anxiolytic, or antipsychotic effects, depending on the needs of the individual patient. Another option to reduce the frequency and severity of side effects is to decrease the opioid dose to the minimum acceptable dose that will still achieve adequate analgesia. Based on the observation that tolerance to opioid-induced nausea accrues rapidly, the dose that had previously been reduced may be titrated upward slowly to increase analgesia without inducing nausea. If nausea is protracted, one may consider changing to a different opioid. The emetogenic response to opioids is idiosyncratic. Therefore a different opioid may not produce nausea.[32]

Pruritus

Opioid-induced pruritus occurs more frequently with opioids delivered via the intravenous or neuraxial route than with oral administration. Tolerance to pruritus usually develops reasonably quickly, but in rare cases, it can be more persistent. The underlying mechanism of pruritus appears to be related to the release of histamine, which activates C-fiber itch receptors on C fibers that are distinct from pain-transmitting C fibers. Clinically, pruritus is often limited to the face and perineum but can become generalized and severe. Treatment includes antihistamines, but the therapeutic effect may be related more to sedation than a direct antihistaminergic effect.[32] In patients receiving intrathecal or intravenous

morphine with significant pruritus that is unresponsive to antihistamines, low dosages of nalbuphine, a μ-receptor antagonist and κ-receptor agonist, may effectively reduce pruritus without reversing the analgesia.[33,34]

Sedation

Opioid-naïve patients or those chronically taking opioids who are undergoing dose escalation often experience sedation and drowsiness. Sedation is usually temporary as patients accommodate a new medication or dose, and it has been demonstrated that patients maintained on a stable dose of opioids for seven days rarely have psychomotor impairment.[35–37] The importance of this fact cannot be overemphasized because the opioid prescription for patients with cancer- and non-cancer-related pain remains substantial, if not decreasing, since the recognition of the opioid crisis. Patients and others may question whether it is safe to operate a motor vehicle while taking opioids. This is a controversial issue, and strong arguments can be made on both sides. Some physicians may recommend taking no precautions, whereas others may counsel their patients to never drive while taking opioids. Emerging evidence is not completely clear on this issue, but some studies have suggested that patients managed with long-term opioid therapy may be alert enough to drive safely.[38,39] However, it seems prudent to restrict driving, at least for one week or longer at the onset or with dose escalation of an opioid regimen.

Despite an adequate adjustment period to the opioid dose, sedation that persists can become as problematic as the pain itself. In such cases, lowering the dose of opioid to the minimally acceptable analgesic level, increasing (widening) the dosing interval, or changing to another opioid that may not be as sedating may be considered.[32] If the sedation is thought to be secondary to accumulating levels of the drug or its metabolites, changing to a different agent that is not as dependent on renal clearance or does not have active metabolites, such as fentanyl, may reduce the sedation. In patients with continued unremitting sedation after limiting CNS depressants, attempting opioid dose reduction, and excluding all other underlying causes, psychostimulants may be useful (e.g. amphetamines, modafinil).

Recent attention has raised the importance of considering sedation associated with other medication-related causes (e.g. benzodiazepines, antiemetics, tricyclics, and anti-convulsants such as gabapentin and pregabalin), renal or hepatic dysfunction leading to accumulation or progression of the patient's primary disease state itself. Gabapentinoids are commonly prescribed for pain, and there are rising concerns that drugs such as gabapentin are abusable and, in conjunction with co-prescribed opioids, may increase the risk of respiratory depression. A 2017 study by Gomes et al. found that concomitant use of gabapentin and opioids was associated with a substantially increased risk of opioid related death.[40] Perioperative use of gabapentinoids may increase the risk of opioid overdose and other opioid related adverse events. There are also increasing concerns that, although gabapentin does not appear to have great addiction potential, it is abused and has illicit use street value.[41] An FDA advisory from 2019 [https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression] stated "Reports of gabapentinoid abuse alone, and with opioids, have emerged, and there are serious consequences of this co-use, including respiratory depression and increased risk of opioid overdose death." In light of this, the FDA has required updated labeling for gabapentinoids to warn against potential respiratory depression. According to the federal government, some states have scheduled gabapentin as a potential drug of abuse, and pregabalin is schedule 4.

Respiratory Depression

Respiratory depression is one of the most serious concerns and feared complications of opioid prescription. The underlying mechanism of respiratory depression is μ-receptor induced depression of brainstem centers that subserve respiratory drive.[42] It has long been recognized to occur more rapidly in patients who have received combined intrathecal-epidural and oral or intravenous opioids. Although there is minimal evidence to support this claim, recognizing that this is a possible risk often supports an acceptable risk management-oriented approach to opioid administration. In addition, combining opioids with other sedating drugs can hasten respiratory depression. This is particularly important because of the escalating rates of unintended overdose deaths associated with opioids, many involving multiple drugs that include additional respiratory depressants such as benzodiazepines. Clinically, the patient manifests sedation as the first sign of respiratory depression, which can pose a problem in detection during the evening hours when the patient is sleeping. Because respiratory depression can occur after the administration of epidural and intrathecal opioids and is often delayed and does not appear until approximately 12 h after injection, the signs of sedation may be lost during sleep. Therefore it is advisable to use alarmed pulse oximetry in patients in whom clinical suspicion is warranted.[32]

Pain is a powerful physiologic stimulant of the respiratory drive and opposes the respiratory depressant effects of opioids. In patients in whom pain relief is anticipated from a non-opioid analgesic treatment (e.g. neurolytic procedure, radiation therapy, adjuvant analgesics, surgery), a reduction in opioid dose may be required.[42]

If a patient cannot be aroused and opioid-induced respiratory depression is suspected, the specific opioid receptor antagonist naloxone should be administered. Care must be taken when administering naloxone to patients who have been taking opioids for longer than one week or older adult patients because severe withdrawal symptoms, seizures, and severe pain can be induced. The administration of naloxone has also led to congestive heart failure in susceptible patients. Naloxone is often packaged in an ampule containing 0.4 mg for intravenous administration, which can then be diluted in 10 mL of normal saline and administered as 0.5 mL boluses (0.02 mg/0.5 mL) every 2 min.[42]

Opioids and Immunologic Effects

Opioids have been suggested to play a role in the incidence of infection in heroin users and contribute to the pathogenesis of human immunodeficiency virus.[27] Of note, despite the suggestion that exogenous opioids may cause immunosuppression, endogenous opioids such as endorphins promote immunoactivation.[27] Inhibitory effects on antibody and cellular immune responses, natural killer cell activity, cytokine expression, and phagocytic activity have all been implicated in acute and chronic opioid administration.[27,41] Furthermore, it has been noted that peripheral immune cells express opioid receptors, which allows intricate communication between cells and cytokines.[27,43] Opioid-induced alteration of immune function can be categorized into central and peripheral components. It has been postulated that central opioid receptors mediate peripheral immunosuppression via the hypothalamic-pituitary-adrenal axis and autonomic nervous system.[27,41,44] Interestingly, severe chronic pain has been suggested to be associated with a reduction in immune function.[27,41,43]

Opioids and Hormonal Changes

The oral, intravenous, and intrathecal routes of administration of chronic opioid therapy have been well-described to alter hormonal effects in both men and women.[27] In illicit drug users, serum hormones that are altered by opioid administration subsequently return to normal following suspension of the drug.[44] Hormones disrupted by opioids are not relegated to testosterone (both total and free) but also include estrogen (estradiol), luteinizing hormone, gonadotropin-releasing hormone, dehydroepiandrosterone, adrenocorticotropin, corticotropin-releasing hormone, and cortisol.[27,45–49] Opioid related endocrinology research focuses on androgen hormones because of the well-described symptomatic side effects. Sexual dysfunction (erectile dysfunction, decreased libido), depression, and fatigue are some of the many side effects that men may experience when prescribed chronic opioid therapy.[27,45,46] Many of the side effects mentioned above have been correlated with hypogonadism. Symptoms such as depression and sexual dysfunction are not relegated to men; women can experience such side effects as well.[27,45,46] Women also experience dysmenorrhea and potentially reduce bone mineral density. Testosterone levels appear to be reduced in women and may be correlated with body mass index.[27,47–48]

Opioid-Induced Sleep Disturbances

A considerable number of studies on the effects of chronic opioid therapy on sleep are still needed. Despite the paucity of data, some studies suggest that opioids increase the number of shifts in sleep-waking states and reduce total sleep time, sleep efficiency, δ sleep, and rapid eye movement (REM) sleep.[27,50–52] In various studies, it is difficult to separate the effect of opioids on sleep from those of comorbid conditions (e.g. cancer, addiction or dependence, postoperative pain). Research suggests that γ-aminobutyric acid (GABAergic) signaling via inhibition of acetylcholine release in the medial pontine reticular formation is the primary focus for the disruption of sleep by opioids.[27,50–52] Morphine has been demonstrated to reduce REM sleep. The resulting disruption in sleep architecture affects the state of arousal during wakefulness.[27,50–52]

Opioid Tolerance and Physical Dependence

Substantial differences that distinguish tolerance, dependence, and addiction from each other. Unfortunately, these concepts are frequently misunderstood. In 2001, the American Pain Society, American Academy of Pain Medicine, and American Society of Addiction Medicine approved definitions of addiction, physical dependence, and tolerance in the hope of reducing misguided treatment of patients who require opioids for pain treatment. In patients who are chronically administered opioids, it should be anticipated that physical dependence and tolerance will develop, but clinicians should remain vigilant for maladaptive changes in behavior witnessed in patients with addiction (see later discussion) while recognizing that these changes only occur in a minority of cases.[53]

Tolerance

The term *opioid tolerance* is often used to describe the phenomenon that occurs when a fixed dose of an opioid results in decreasing analgesia, thus requiring higher doses of medication to achieve the same or less effect over time.[32] Because some opioids are only appropriate for use in opioid tolerant patients, for practical purposes, the FDA has defined a patient who is opioid tolerant as one who has received at least 60 mg oral morphine equivalents for at least seven days. The mechanisms responsible for this phenomenon are not entirely understood, but the *N*-methyl-D-aspartate (NMDA) receptor has been demonstrated to be involved.[54,55] The clinical usefulness of NMDA receptor involvement has yet to be determined fully, but nonhuman studies have continued to promulgate the potential for using NMDA receptor antagonists in conjunction with opioids to attenuate tolerance and physical dependence.[56,57] A subpopulation of dorsal horn neurons expressing NMDA receptors and treated with high-dose morphine have been shown to have enhanced NMDA receptor-mediated activity.[56] Furthermore, μ-receptor antagonist and NMDA receptor antagonist treatment of this subpopulation have attenuated the increased activity.[56] Another study has demonstrated that in "morphine-tolerant" rats treated with an NMDA receptor antagonist, the morphine-induced tolerance reversed.[57] The relevance of these findings at the bedside have, to date, not been clear.

Human studies on the effects of NMDA receptors on tolerance have been less promising. There has been great hope that NMDA receptor antagonists such as ketamine or dextromethorphan might potentiate the analgesic effect of opioids, but no convincing evidence has emerged from replicated trials.[58,59] In a double-blind controlled clinical trial comparing morphine and a combination of morphine and dextromethorphan, statistical differences in analgesia or dose were not seen between groups.[60] Nonetheless, basic concepts continue to support the understanding that the NMDA receptor is a key component in the development of opioid-induced tolerance. In particular, ketamine continues to be a drug of major interest because of its potential to improve opioid performance by preventing tolerance and enhancing opioid-induced analgesia.[61–63]

When a patient is suspected of having become tolerant to one medication, the cause may be that the pain is not sensitive to opioids, the patient has become opioid tolerant, or it may be related to increased pain, which requires adjustment in dosing. The need for dose escalation in patients treated with chronic opioids should constantly stimulate consideration of the progression of the underlying disease. Opioid rotation can be performed when opioid-induced tolerance is present. This is based on the clinical observation that patients often have intraindividual analgesic responses to different opioids and that improved analgesia with fewer side effects may occur when a different opioid is used.[64] Although the full mechanism of this phenomenon is not completely understood, it is usually thought to occur because of incomplete tolerance, possibly related to differing μ-opioid and other opioid receptor affinities of one opioid versus another. When opioid rotation is performed in opioid tolerant patients as opposed to opioid-naïve patients, equal analgesic doses may not be necessary. The patient may respond with analgesia to half the equianalgesic dose, and if not, the dose may be titrated to an adequate analgesic effect that is less than would be expected by calculation of equianalgesic conversion from standard formulas. This is a potentially useful phenomenon whereby the overall opioid requirement of the patient may be reduced, thereby achieving an opioid-sparing effect.

Physical Dependence and Withdrawal

Physical dependence is a physiologic state that occurs when a medication is abruptly stopped and withdrawal syndrome results. This is *not* synonymous with addiction. This separation of physical dependence and addiction is supported by evidence of two distinct anatomic areas within the CNS that are involved in physical

dependence versus addiction. Noradrenergic neurons within the locus coeruleus are implicated in the maintenance of dependence and development of withdrawal, whereas the ventral tegmental dopaminergic area and orbitofrontal glutamatergic projections to the nucleus accumbens are thought to subserve addiction.[61,65] It has been shown that drugs of abuse such as heroin, cocaine, nicotine, alcohol, phencyclidine, and cannabis initiate habit-forming actions by activating a common reward pathway in the brain.[66] There is also well as the involvement of noradrenergic neurons in the development of withdrawal. Not only do norepinephrine levels change in the brain following opioid dependence, but the administration of an α_2-agonist such as clonidine or a β-antagonist such as propranolol also attenuates many of the symptoms of opioid withdrawal but does not reverse addiction.[67]

The clinical manifestations of opioid withdrawal usually begin with irritability, anxiety, insomnia, diaphoresis, yawning, rhinorrhea, and lacrimation. If it progresses without intervention, a flu-like condition develops, with chills, myalgia, fever, abdominal cramping, nausea, diarrhea, tachycardia, and other features of a heightened adrenergic state. Although uncomfortable for patients, it is self-limited and lasts approximately three to seven days. Opioid withdrawal may occur in patients who abruptly discontinue opioids or who have relative discontinuation because of taking SAOs after accommodating the longer plasma half-life of LAOs.[32]

It is usually possible to taper patients from opioids without inducing withdrawal symptoms. Although faster tapering can be accomplished without the advent of withdrawal symptoms, if time allows, few patients will be symptomatic if the dose is decreased by 10%–20% every 48–72 h over a prolonged period (usually two to three weeks, depending on the dose).[68] If withdrawal symptoms develop during discontinuation or taper, clonidine, 0.2–0.4 mg/day, may be used to decrease discomfort.[69] Clonidine is often maintained for four days during taper of an SAO and 14 days during taper of an LAO. Once opioids have been discontinued, clonidine can be tapered for approximately one week.[32]

Other medications are also used for managing withdrawal symptoms, often drugs with GABA B receptor antagonism (i.e. tizanidine) and/or α_{2A} adrenergic receptor agonists (i.e. lofexidine or tizanidine).

Opioid Use Disorder

Opioids are associated with substance abuse at a rate that is high enough to be a significant concern. However, the exact rate of opioid use disorder as a result of therapeutic opioid use is controversial. Opioid use disorder (OUD) is characterized by opioid use that results in physical, psychological, or social dysfunction (or a combination of these) and continued use of opioids despite the dysfunction. The DSM-5 defines OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress, with at least a 12-month period of at least two of the 11 symptoms (Box 48.1).

Neurobiologic evidence has suggested that OUD may be subserved by positive reinforcement and sensitization of the dopaminergic system in the brain, which may explain the continued seeking of a substance destructive to the patient's life.[70] Patients who are receiving an inadequate dose of opioid medication may engage in drug-seeking behavior to obtain more pain medication for the relief of pain, which can be mistaken for the drug-seeking behavior associated with OUD. Physicians are often challenged to distinguish true use disorder from undertreated pain because undertreated pain may appear similar to OUD because of features such as drug-seeking and self-escalation. However, unlike OUD, undertreated patients experience pain relief and improved function with increased doses of opioids. OUD directly contrasts with what is seen in a patient with undertreated pain who goes through dose escalation. With OUD, aberrant behavior not only continues despite an increase in opioids but is also usually further stimulated and promoted by increased exposure to the addicting drug. The Committee on Pain of the American Society of Addiction Medicine has defined OUD in the context of pain treatment with opioids as a persistent pattern of dysfunctional opioid use based on a comprehensive clinical assessment that includes history, physical examination, validated clinical scales that measure withdrawal symptoms, and urine drug testing.[71] Patient behavior may be used cumulatively to support the diagnosis of addiction, but absolute conclusions cannot always be made, particularly without longitudinal information over extended periods. Many types of behavior may indicate the possibility of addiction (Box 48.2).

• BOX 48.1 Eleven Symptoms in Opioid Use Disorder

Taking opioids in larger amounts or over longer periods than intended
Having a persistent desire to control opioid use
Sending excess time obtaining, using, or recovering from opioid use
Having opioid cravings
Inability to fulfill work, home, or school responsibilities from continued opioid use
Continued opioid use despite persistent interpersonal problems
Lack of involvement in social, occupational, or recreational activities
Opioid use in physically hazardous situations
Continued opioid use despite persistent physical or psychological problems
Tolerance, including the need for increased amounts of opioids
Opioid withdrawal syndrome
The DSM-5 defines OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress, with at least a 12-month period of at least two of the 11 symptoms.

Nonadherence to opioid therapy may be related to many possibilities, including adverse effects, forgetfulness, incompatibility with lifestyle, and confusion about the drug regimen. It may rarely be related to aberrant behavior such as diversion or drug abuse, and an astute physician will maintain a position of vigilance without feeling compelled to reach immediate conclusions. If a physician chooses to pursue pain treatment with an abusable drug in a patient at risk for addiction, collaboration with an addiction specialist or addiction psychiatrist is advised to ensure that the necessary resources to support an appropriate risk management program are available. Such resources are usually far greater than those available to the average prescriber, and without the necessary resources to ensure safety, prescribing should not begin. High vigilance and tempered judgments are always required.

The exact rates of opioid misuse and abuse in patients with chronic pain are not exactly known. However, estimates range from 1%–40%.[72] Treating chronic pain in a person with a history of substance use disorder is challenging and highly risky, but it is not absolutely contraindicated. Nonetheless, responsible prescribers of opioids must ensure that the appropriate resources for safe use are in place before initiating treatment. If appropriate risk management is not available, treatment should not be initiated. Moreover, treatment should not be initiated unless it can be terminated when necessary.

Although a low percentage of the population with chronic pain appears to experience addiction, the remainder of the population has been shown to be at risk for receiving suboptimal analgesia because of prescribers' fears of patient abuse of the opioid.[73] A

• Box 48.2 Aberrant Behavior Indicative of Addiction

Behavior *Less* Indicative of Addiction

Expresses anxiety or desperation over recurrent symptoms
Hoards medications
Takes someone else's pain medications
Aggressively complains to the physician for more drugs
Requests a specific drug or medication
Uses more opioids than recommended
Drinks more alcohol when in pain
Expresses worry over changing to a new drug, even if it offers potentially fewer side effects
Takes (with permission) someone else's prescription opioids
Raises the dose of opioids on one's own
Expresses concern to the physician or family members that pain might lead to the use of street drugs
Asks for a second opinion about pain medications
Smokes cigarettes to relieve pain
Has used opioids to treat other symptoms

Behavior *More* Indicative of Addiction

Buys pain medications from a street dealer
Steals money to obtain drugs
Tries to get opioids from more than one source
Performs sex for drugs
Sees two physicians at once without them knowing
Performs sex for money to buy drugs
Steals drugs from others
Prostitutes others for money to obtain drugs
Prostitutes others for drugs
Forges prescriptions
Sells prescription drugs

From Passik SD, Kirsh KL, Donaghy KB, et al. Pain and aberrant drug-related behaviors in medically ill patients with and without a history of substance abuse. *Clin J Pain* 2006;22:173–181.

growing debate has emerged that focuses on understanding how opioids should be used in the setting of substantial rates of chronic pain while balancing the imperative for vigilant use of opioids with sufficient risk management for acceptable safety.

If the decision is made to prescribe opioids, it is imperative to prescribe an opioid antagonist, most commonly intranasal naloxone, as a potentially life-saving antidote for patients with OUD. The United States FDA recommends making naloxone available to all patients with opioids. However, it is especially important to prescribe naloxone for those at increased risk of opioid overdose (patients with a history of OUD, patients with concomitant use of other CNS depressants, and patients with a history of opioid overdose).

Selected Opioids

Although therapeutic options to provide analgesia continue to emerge, opioids remain the "gold standard" of currently available analgesics**.** Despite the widespread use of opioids to treat acute and chronic pain, controversy exists regarding the use of opioids for the treatment of chronic nonmalignant pain. There are proponents on each side of the controversy, and part of the fear of prescribing opioids stems from an inaccurate understanding of appropriate outcomes for prescribing opioids and the risk of abuse or side effects. Although opioids can be a useful tool to provide adequate analgesia for patients, fear of the development of OUD, dependence, or untoward side effects often precludes physicians from prescribing opioids.[74] If it is decided to initiate opioid therapy in patients with chronic nonmalignant pain, the decision should be based on a well-thought-out rationale for treatment, with clear end points in mind.

If the decision is made to initiate opioid therapy, SAOs are generally preferred for the initial phase of management of chronic and non-cancer acute pain. LAOs are typically reserved for patients on well-established dosing and amounts of opioids. SAOs should be titrated slowly to the lowest effective dose, in increments of 25%–50% of the total daily dose. Generally, in treating chronic pain, expert guidelines generally suggest avoiding dosages above 90 mg or morphine mg equivalents given the increased risk of overdose and other adverse effects with higher dosages and lack of evidence for increased analgesia with excessive dosages. Guidelines now suggest avoiding high doses or quantities of opioids given the increase in the prevalence of OUD among the general population. SAOs are often initially prescribed for patients with chronic pain syndromes because they have relatively brief peak serum blood levels of active analgesic metabolites. However, the use of SAOs to treat persistent baseline chronic pain may require frequent dosing. This roller coaster effect is thought to promote nonoptimal pain related behavior, which is why LAOs have been used once the total opioid dose requirement is well-established in such cases. Nonetheless, science has not clearly demonstrated this advantage.

SAOs are often combined with other analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or aspirin, which may offer drug-sparing effects because less medication may be used. Although combination opioids may help reduce opioid related side effects and toxicity, there is a potential for harm to major organs from non-opioid components (e.g. acetaminophen, NSAIDs, aspirin). When using combination opioids, physicians must be aware of renal and liver function problems, as well as the potential harm that could occur in the GI system. Patients must be educated about the risks of taking other analgesics, such as acetaminophen, NSAIDs, and aspirin, in conjunction with the combination opioids. Moreover, physicians must also consider that non-opioid drugs are likely to have a ceiling effect beyond which they are no longer efficacious. Because opioids induce tolerance and have no ceiling effect, the pharmacologically appropriate need for increased opioids may inadvertently push the dose of a combination drug to appropriate levels of the opioid component but to toxic levels of the non-opioid agent. Although reviewing all available opioids is beyond the scope of this chapter, we will review some of the most commonly used opioids for pain management. Minor opioids, such as hydrocodone, are discussed in Chapter 49.

Codeine

Codeine is an alkaloid found in very low concentrations in opium. It is now derived from morphine. Codeine is frequently administered in combination with acetaminophen, butalbital, and caffeine.[69] It has been shown to be an effective analgesic for chronic nonmalignant pain but has limitations.[75] It is a weak μ-opioid agonist and has a half-life of 2.5–3 h. The major metabolic pathway leads to glucuronidation of codeine to codeine 6-glucuronide, with a minor metabolic pathway catalyzed by the polymorphically expressed enzyme CYP2D6 through *N*-demethylation of codeine to norcodeine and *O*-demethylation of codeine to morphine.[10] Evidence has suggested that the analgesic effects of codeine rely on its conversion to morphine, and patients with genetic variations in the enzymes needed to make this conversion may find codeine to be less effective.[76] The genetic polymorphism of

CYP2D6 is responsible for the variable response to the medication. Patients with the genotype CYP2D6 PM (poor metabolizers) do not achieve adequate analgesia with codeine. In addition, certain medications that inhibit CYP2D6, such as quinidine, paroxetine, fluoxetine, and bupropion, can alter the phenotype of normal patients with normal genetics and thus decrease the therapeutic analgesic effect of codeine.[77] Urinary excretory products of codeine include codeine (70%), norcodeine (10%), morphine (10%), normorphine (4%), and hydrocodone (1%).[69] This may be important to remember when interpreting the urine toxicology screens of patients taking codeine.

Morphine

Morphine, a hydrophilic phenanthrene derivative, is a prototypical opioid against which all other opioids are compared for equianalgesic potency. Because of its hydrophilic nature, it exhibits delayed transport across the blood-brain barrier, thus delaying its onset of action. Conversely, it has a longer duration of action, 4–5 h, than its plasma half-life of 2–3 h.[25] Metabolism of morphine to its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), occurs mainly in the liver (see Table 48.1). Although the parent compound produces analgesia and side effects, M6G may also produce some analgesia along with some adverse effects. M6G accounts for 5%–15% of morphine metabolites and is a μ- and δ-agonist, which accounts for its analgesic effects. It has been demonstrated that M6G does not exert antinociceptive effects in knockout mice lacking the μ-receptor.[78]

M3G, which accounts for 50% of morphine metabolites, does not appear to possess opioid agonism but may produce effects that oppose morphine's analgesic actions, such as allodynia, hyperalgesia, myoclonus, and seizures.[10] Oral administration of morphine has been shown to result in higher levels of M3G and M6G than those achieved with the intravenous, intramuscular, or rectal routes, which bypass hepatic metabolism.[79] Chronic administration of morphine ultimately results in higher circulating levels of M3G and M6G metabolites than the parent compound.[80] It has been found that patients receiving chronically high morphine doses metabolize morphine to hydromorphone and test positive for hydromorphone on urine toxicology screens.[81] This is of critical importance in patients using morphine for chronic pain who undergo urine drug screening.

Although extrahepatic metabolism of morphine has been shown to occur in gastric and intestinal epithelia, morphine should be used with caution in patients with decreased hepatic function, such as those with cirrhosis.[10] In addition, glucuronides have been shown to undergo deconjugation back to the parent compound by colonic flora and reabsorbed as morphine.[10] Morphine metabolites are excreted by the kidneys, so caution should also be taken when prescribing morphine to patients with renal impairment because the accumulation of M6G and M3G can be toxic. Available forms of morphine include short- and long-acting preparations. Short-acting agents may be compounded for almost any route of administration, and long-acting preparations generally use specialized sustained release matrix technologies, such as those found in MS Contin, Kadian, Oramorph SR, and Avinza.

Oxycodone

Oxycodone is a semisynthetic opioid that is closely related to morphine. It has been available for analgesia since 1917 when it was introduced into clinical practice in Germany.[82] It is processed from thebaine, an organic compound found in opium. Similar to morphine, currently available forms of oxycodone include short- and long-acting preparations. Short-acting oxycodone may be used alone (e.g. Roxicodone) or may be compounded with acetaminophen (e.g. Percocet, Roxicet, Endocet) or aspirin (e.g. Percodan). Long-acting oxycodone preparations are designed for oral administration and involve the use of specialized sustained release technology (e.g. OxyContin, Xtampza, and similar generics).

Oxycodone has a bioavailability of 60% compared with morphine, which has a bioavailability of 33%, thus making oxycodone almost twice as potent as morphine.[70] Oxycodone is a prodrug that undergoes hepatic metabolism via the CYP2D6 isoenzyme, whereby it is converted into its active metabolite oxymorphone, a μ-opioid agonist, and its inactive metabolite noroxycodone. Oxymorphone is reportedly often undetectable and is 14 times more potent than the parent compound.

Similar to codeine, there is genetic polymorphism in 10% of the population, which accounts for significant variation in the metabolism of oxycodone. This variation explains why some patients require higher than usual doses of oxycodone to achieve analgesia. Another factor to be considered when prescribing oxycodone is whether other potential competitors of the CYP2D6 isoenzyme are being prescribed. Such interacting medications include neuroleptics, tricyclic anti-depressants, and selective serotonin reuptake inhibitors (SSRIs). Cases of serotonin syndrome have been described in the literature when SSRIs and oxycodone were used concomitantly.[83,84]

TABLE 48.1 Selected Opioids: Oral Bioavailability, Half-lives, Duration of Action, and Metabolites

Opioid	Availability (%)	Half-life (h)	Duration of Action (h)	Metabolites
Morphine	10–45	2–3	4–5	M6G, M3G
Oxycodone (OxyContin)	60–80	4.5	12	Oxymorphone, noroxycodone
Methadone	60–95	8–80 (average, 27)	6–8	—
Hydromorphone	24	2.3	3–4	H3G
Oxymorphone (Opana ER)	10	9 ± 3	12	O3G, 6-hydroxyoxymorphone

H3G, Hydromorphone 3-glucuronide; *M3G*, morphine 3-glucuronide; *M6G*, morphine 6-glucuronide; *O3G*, oxymorphone 3-glucuronide.

Meperidine

The use of meperidine for analgesia has been declining recently because of its potential neurotoxicity. It is a weaker μ-opioid agonist than morphine with 10% potency, more rapid onset, and a shorter duration of action,[85] with a half-life of 3 h, and it is hepatically demethylated to its neurotoxic metabolite normeperidine, which has a half-life of 12–16 h. Normeperidine has been well-documented to cause CNS hyperactivity and seizures.[25] Its excretion occurs via the kidneys. Therefore caution should be taken when administering meperidine to patients with renal impairment or those prone to CNS hyperactivity. Initially, the toxic effects may be seen as subtle changes in mood that can progress to naloxone-irreversible tremors, myoclonus, and seizures. Chronic administration of meperidine to patients with normal renal function and administration of meperidine in conjunction with SSRIs, monoamine oxidase inhibitors, tramadol, and methadone can also result in neurotoxic side effects.

Hydromorphone

Hydromorphone has a strong affinity for the μ receptor. It is a hydrogenated ketone analog of morphine and can be formed by *N*-demethylation of hydrocodone.[85] Hydromorphone is similar to morphine in that it is hydrophilic and has a comparable duration of analgesia, but it differs regarding side effects and potency. Pruritus, sedation, nausea, and vomiting occur frequently. Hydromorphone is five times more potent than morphine when administered orally (see Table 48.2) and seven times more potent when administered parenterally. Though essentially hydrophilic, it is ten times more lipophilic than morphine. This lipophilicity may be advantageous when treating patients who cannot take oral medications and cannot maintain intravenous access, such as in hospice environments. It can be administered subcutaneously at a dose of 10–20 mg/mL; this route delivers approximately 80% of the dose absorbed through intravenous delivery.[85] The onset of analgesia occurs within 30 min after oral administration and 5 min after intravenous administration, with peak analgesic effects occurring within 8–20 min.[85]

TABLE 48.2 Equianalgesic Doses of Opioids

Opioid	Oral Equianalgesic Dose (mg)
Buprenorphine	0.3
Oxymorphone	1.5
Butorphanol	2
Hydromorphone	2
Oxycodone	7
Hydrocodone	10
Morphine	10
Methadone	10–20
Tramadol	40
Codeine	80
Meperidine	100

Hydromorphone is metabolized in the liver to H3G, and like its parent compound, it is excreted renally. Like M3G, H3G lacks an analgesic effect but may be an active metabolite that potentiates neurotoxic effects such as allodynia, myoclonus, and seizures.[10] The production of H3G is relatively low. Hence, the risk of neurotoxic side effects is relatively low, except in patients with renal insufficiency, in whom H3G may accumulate.[81]

Fentanyl

Fentanyl is a highly lipophilic agent with a high affinity for the μ-opioid receptor. It is 75–125 times more potent than morphine and has a faster onset of action.[80] Because of its higher potency, smaller quantities of the medication can be delivered to the patient relative to other opioids. Although fentanyl is considered a short-acting medication, its lipophilic nature allows long-acting transdermal and very rapid onset transmucosal administration to treat chronic and acute pain, respectively.[86,87] Although there are other minor pathways, fentanyl undergoes hepatic biotransformation via CYP3A4 *N*-dealkylation to norfentanyl. Its half-life and onset of action vary greatly depending on the route of administration. (Transmucosal fentanyl undergoes first-pass metabolism and has an onset of action within 5–10 min.)[88]

A transdermal fentanyl patch is used in some patients with chronic pain or pain related to cancer. Transdermal fentanyl has been used for acute postoperative pain but may be associated with hypoventilation.[87] Transdermal patches are typically placed on a hairless part of the body that is flat and free of any defects that could interfere with patch adherence. Patients should be advised to avoid submerging the patch in hot water or placing a heating pad over the area because this influences absorption. Patients report local skin erythema or irritation as the most common side effect.[87]

Transdermal fentanyl is an alternative choice for patients with significant GI issues, such as persistent emesis, chronic nausea, or "short gut" syndrome, or for those believed to be at risk of diverting oral medications. The use of the patch offers the opportunity to allow patients to return the old patches for inspection at the time of prescription refill. Theoretically, transdermal delivery may induce less constipation than oral opioids because it avoids direct exposure to the GI tract, but this is questionable in light of the common finding of significant constipation in almost all patients who use transdermal opioids.

Unlike other LAOs, transdermal fentanyl may be challenging to titrate because of variations in individual patient characteristics, such as skin perspiration, skin temperature, fat stores, and muscle bulk.[10] The rate of achieving therapeutic serum levels can vary (ranging from 1–30 h with a mean of 13 h). Because of the wide variation in reaching therapeutic levels, a short-acting oral analgesic or intravenous patient-controlled analgesia may be necessary to address breakthrough pain, while the transdermal opioid effect is ramping up or to prevent withdrawal symptoms if rotation from another opioid has occurred. Achieving steady state levels may require up to six days, and the amount of SAO needed after a steady state is attained will help determine whether the dose of fentanyl must be increased.[10] However, if the patch is removed, it may take up to 16 h for serum fentanyl concentrations to drop by 50%.

Oral transmucosal fentanyl has a more rapid onset of analgesia than other SAOs and offers some advantages. Because it is transmucosal, it avoids the GI tract and first-pass hepatic metabolism and has a rapid onset of action within 10–15 min. One study

compared intravenous morphine with transmucosal fentanyl in an acute postoperative setting and demonstrated a similar onset of analgesia.[88] Transmucosal fentanyl can be beneficial for patients with acute breakthrough pain. To date, a major limitation in using this route is the cost.

Methadone

Methadone may be an attractive choice for analgesia because of its unique properties, but it also has many features distinguishing it from other opioids that have raised its potential for adverse outcomes. Methadone has become the most common opioid found to be related to unintended overdose deaths in the United States. Thus caution should be exercised with this drug. On the positive side of the methadone risk-benefit profile, its attributes include no known neurotoxic or active metabolites, high absorption and bioavailability, and multiple receptor activities, including μ- and δ-opioid agonism, NMDA antagonism, and serotonin reuptake blockade. Methadone has been shown to have a bioavailability that is approximately threefold that of morphine.[89,90] In patients who require high-dose LAOs, methadone appears to be a theoretical second-line choice despite the lack of accumulation of neurotoxic metabolites that induce myoclonus, hallucinations, seizures, sedation, and confusion. Unfortunately, the unique pharmacokinetics and pharmacodynamics of methadone render its effects somewhat unpredictable.

Methadone is structurally unrelated to other opioid-derived alkaloids. It is a racemic mixture of two enantiomers, the D-ISOMER (*S*-methadone) and THE L isomer (*R*-methadone). *R*-Methadone accounts for its opioid receptor affinity and thus its opioid effect. Animal studies have demonstrated that methadone has a lower affinity than morphine for the μ-receptor.[91] This may explain why methadone may have fewer μ-opioid related side effects than morphine. However, methadone has a higher affinity for the δ receptor than morphine.

Methadone has a slow but variable elimination half-life that averages approximately 27 h, which may be related to its lipophilicity and extensive tissue distribution.[91] The delayed clearance of methadone is the basis for its use in maintenance therapy. Surprisingly, although methadone may be efficacious for the purpose of opioid maintenance therapy because it potentially prevents withdrawal symptoms for 24 h or longer, its analgesic half-life is shorter than 24 h, usually found to range from 6–8 h. This discrepancy is related to the biphasic elimination. The α elimination phase lasts 8–12 h and correlates with the period of analgesia, which lasts approximately 6–8 h. The β elimination phase ranges from 30–60 h and is responsible for preventing withdrawal symptoms; this property is exploited in maintenance therapy.[91]

Methadone has multiple drug interactions related to inducers or inhibitors of the CYP system, particularly the 2D6 and 3A4 subtypes.[92] Because these interactions rarely are seen with other opioids, drug interactions with methadone may not be as readily anticipated or detected. Besides interacting with drugs, 3A4 is an auto-inducible enzyme, which accounts for the fact that methadone can bring about its own metabolism and increase its clearance with prolonged use.[91,92]

Other issues affecting methadone absorption and accumulation are gastric and urinary pH. Decreased gastric pH, such as in patients taking proton pump inhibitors, results in increased rates of methadone absorption. Renal failure and hemodialysis do not alter the excretion of methadone. However, as urinary pH increases, methadone clearance in urine decreases. Urine pH higher than six can reduce methadone clearance from 30% to almost 0%, thereby resulting in increased circulating levels. Most methadone is eliminated in feces.[10] Another source of methadone's potential metabolic instability relates to its avid protein binding. Acute changes in protein binding may lead to sudden increases or decreases in circulating methadone levels.

The difference between methadone and other LAOs is that the duration of the effect of methadone is intrinsically long-acting, whereas most other LAOs are sustained-released forms based on compounding technology. This is beneficial for patients with impaired GI absorption. In addition, methadone is available as a powder, allowing it to be formulated for almost any route of administration. Methadone pills can be broken and cut in half, and it is also available as a liquid elixir (1 or 10 mg/mL). This avoids the need to crush pills, which offers a potential advantage in patients with gastrostomy tubes. In addition, because methadone elixir has a low-concentration formulation, careful and precise titration of methadone can be performed to achieve adequate analgesia.

One of the most disturbing aspects of methadone use in the United States has been the reported increase in methadone-related deaths.[93,94,95] Although the mechanism for these deaths is not exactly clear, many appear to be related to overdose and drug interactions. In some cases, an overdose may be related to misunderstanding the standard conversion rates of methadone from other opioids. Contrary to conventional wisdom, methadone appears to be more potent (milligram for milligram) in patients whose treatment is being switched to methadone from high doses of other opioids. Although standard conversion tables may suggest that the ratio of conversion from morphine to methadone may be from 1:1 to 1:3, these ratios were taken from studies on acute pain or normal controls. Many of these conversion tables were developed over 20 years ago, far before recent increases in methadone use as a chronic analgesic. If much higher pre-switch dosages are converted to methadone, the appropriate morphine to methadone ratio may range from 1:5 to 1:20 or higher. Such a counterintuitive dosing phenomenon leads to the potential for overdose.

Another possible source of methadone-related mortality includes torsade's de pointes arrhythmias, which have been reported in some patients.[96] Although a prospective study has demonstrated QT prolongation on electrocardiogram in patients taking methadone, it was also concluded that the magnitude of the increase is less than that with other antiarrhythmic drugs and is not higher than the QT widening caused by other drugs, such as tricyclic anti-depressants.[96] The use of methadone requires awareness of possible QT prolongation and the possible additive effect that other QT-prolonging agents may have when combined with methadone. Table 48.1 shows the oral bioavailability, half-life, duration of action, and metabolites of selected opioids. Table 48.2 shows the equianalgesic doses of the different opioids.

Methadone must be used with significant knowledge of the special properties that predispose it to substantial risk. Slow-dosing titration and careful monitoring are essential for safe use. If this and all other elements of safe prescription of opioids are not possible, the drug should not be prescribed.

Buprenorphine

Buprenorphine demonstrates a high binding affinity and mixed agonist-antagonist activity at opioid receptors. A derivative of the morphine alkaloid thebaine, a semisynthetic opioid, possesses unique pharmacologic characteristics compared to traditional opioids, making it an appealing first choice option for chronic pain.

Buprenorphine is a μ-opioid receptor agonist, a κ-opioid receptor antagonist, and is thought to act as a mild antagonist of the δ-opioid receptor. Antagonistic activity at the κ-receptor is believed to explain buprenorphine-associated anti-hyperalgesia, lessened sedation, euphoria, cravings, and dysphoria compared with conventional opioids, and its potential to act as an antidepressant. Distinctively, buprenorphine has been shown to activate the opioid receptor-like (ORL-1) receptor, which may account for a reduction in the development of opioid tolerance. Acting as a "chaperone" ligand, buprenorphine demonstrates the ability to boost μ-opioid receptor expression on cell membranes.

Buprenorphine is a Schedule III controlled substance available in multiple dosage forms, including injection (IV, depo-SC, subdermal implant), transdermal, buccal, and sublingual routes. Buprenorphine is available independently or combined with naloxone in a 4:1 ratio. The addition of naloxone (an opioid receptor antagonist) to sublingual routes is intended to deter misuse and blunt opioid agonist effects if injected. The oral bioavailability of buprenorphine is poor (10%) because of high first-pass hepatic clearance. Buprenorphine is metabolized in the liver through cytochrome CYP3A4 to norbuprenorphine and is excreted primarily through feces. For patients with renal failure, buprenorphine is a preferred opioid analgesic; drug clearance is unchanged with renal impairment and is not removed by dialysis.

Compared to traditional opioids, buprenorphine has an advantageous safety profile. Most notably, when used alone, buprenorphine exhibited a ceiling effect related to respiratory depression. It is essential to understand that when combined with respiratory depressants such as alcohol or benzodiazepines, this protective effect is diminished. Adverse effects such as constipation, sedation, hypogonadism, and tolerance are also seen to be less of a degree with buprenorphine than with other opioids.

Similar to methadone, buprenorphine is an effective treatment for OUDs and opioid dependence. Buprenorphine exhibits slow dissipation from opioid receptors, and sublingual formulations have a prolonged plasma half-life (24–72 h). Delayed drug clearance and high lipophilicity make buprenorphine an ideal agent to prevent withdrawal symptoms, often for a period of up to three days. Interestingly, similar to methadone, buprenorphine displays a shorter analgesic half-life (6–8 h) and is often dosed two to four times daily for pain. It should be clarified that a Data-2000 waiver (additional prescriber training for addiction medicine) is needed to prescribe buprenorphine for OUD but is not required to prescribe buprenorphine for pain.

As attractive as buprenorphine may be for chronic pain as a first choice opioid, compared with a full agonist opioid, logistical limitations exist around prescribing the drug itself. Challenges include a lack of coverage and reimbursement by third-party payers and hospital formularies, as well as a lack of education on the proper usage of buprenorphine. Clinical experience is recommended when transitioning a patient from a full-opioid agonist to buprenorphine. Careful timing of the window of clearance of the initial full-opioid agonist is necessary to prevent abrupt displacement by buprenorphine. The absence of this consideration may lead to severe precipitated withdrawal. Additionally, the equianalgesic data for buprenorphine are conflicting and incomplete.

Conflict exists in the literature on whether to maintain the classification of buprenorphine as a "partial agonist" opioid. Buprenorphine displays low intrinsic activity *in vitro*, leading to a ceiling effect on analgesia in animal models and a ceiling effect on respiratory depression in humans. The question remains as to how this translates clinically. Some studies have shown bell-curve antinociception, while others have observed similar analgesic values to full μ-opioid agonists, such as morphine and fentanyl. The variability of interindividual responses to different opioids remains reliable. The clinical decision to utilize one opioid over another should be made with patient-specific circumstances in mind.

Rational Opioid Prescribing

Opioids work for some pain but not all. They may be problematic for many and even life-threatening for some but knowing who is susceptible is not always clear. Treatment of substantial pain may necessitate the use of opioid related medications. Opioids are not the first choice, nor should they necessarily be the last choice in the pain management armamentarium. A detailed diagnosis with a thorough history and physical examination and an essential focus on risks and benefits will drive the selection of specified analgesic treatments. Non-opioid treatments will often be the initial choice. The decision to use opioid therapy has undergone intense scrutiny as the public health epidemic of prescription drug abuse has been elevated to a national discussion. The importance of risk management with focal attention to the risk-benefit ratio for safe use of opioids underscores the serious potential for opioid abuse and overdose death that has been well documented through approximately 15 years of retrospective data. A history of psychiatric comorbidity and a history of substance abuse are known variables suggestive of increased risk for abuse and unintentional overdose death. A full discussion of the safe prescribing of opioids is beyond the scope of this chapter but can be found in other resources, such as from the Department of Health and Human Services [https://www.hhs.gov/opioids/prevention/safe-opioid-prescribing/index.html], from the CDC Guideline for Prescribing Opioids for Chronic Pain [https://www.cdc.gov/drugoverdose/prescribing/guideline.html], and from the FDA [https://www.fda.gov/consumers/consumer-updates/guide-safe-use-pain-medicine].

Before initiating opioid therapy, a detailed evaluation is necessary. This evaluation must include risk stratification, assessment of functional activity, a thorough review of the patient's medical history with special attention paid to previous experience with opioid analgesics, and a review of other related comorbid factors, including previous substance abuse, mental illness, hepatic, renal, or pulmonary dysfunction, or sleep apnea. Informed consent is a critical element of opioid treatment that requires patient education regarding the benefits and risks associated with treatment. The expectations and responsibilities of patients must be clarified early. Monitoring and management of opioid-induced side effects are imperative. The use of opioid agreements, urine drug screens, and well-defined boundaries of care must be considered before initiating treatment, as well as an exit strategy if treatment fails to be successful for a variety of reasons.

If the patient is opioid-naïve and the benefits outweigh the risks, low-dose SAOs such as hydrocodone or oxycodone may be initiated and carefully titrated to establish an opioid requirement. Because of the rapid clearance and brief half-life of SAOs, toxic accumulation of the medications is less likely than with LAOs. The severity and duration of the patient's pain should help guide whether PRN or fixed dosing is required. In patients with acute pain secondary to an injury or surgery for which rapid healing is expected, PRN dosing is reasonable. However, in patients with the expectation of prolonged recovery or with chronic pain and significant baseline or persistent pain, opioids may be administered in fixed dosing intervals and PRN intervals for breakthrough pain.

Scheduled dosing decreases clock-watching anxiety and reinforcement of pain behavior. However, it may cause drug accumulation. If a patient can tolerate an SAO and its side effects, consolidation of the daily opioid requirement into an equianalgesic LAO regimen may be an appropriate step.

Although opioids may be excellent analgesics, they are often used as a second-line treatment for chronic pain, mainly because chronic pain may respond to non-opioid treatments that might carry fewer risks. When other pharmacologic, rehabilitative, or interventional procedures are not appropriate or are unsuccessful, chronic opioid therapy should be considered. It is not uncommon to combine opioid treatment with other modalities, including psychological and physical rehabilitation. Simultaneously, interventional pain procedures and adjunctive analgesics may be useful.

The effectiveness of opioid therapy for certain types of chronic pain, such as neuropathic pain, remains controversial. Because anti-depressants and anti-convulsants have been shown to provide less than 50% pain relief on average, opioids have been used to treat chronic neuropathic pain despite their narrow therapeutic window.[97] When treating neuropathic pain, it has been shown that opioid potency may be relatively lower than that for other conditions. This seems to be secondary to the changes that occur in the endogenous opioid system after nerve injury. It appears that endogenous peptide levels and opioid receptor density decrease in nociceptive pathways.[97] It also appears that GABAergic tone decreases after nerve injury and that the inhibitory effect of morphine on dorsal horn neuron projections after nerve injury is reduced compared to its effect on non-injured nerves.[98] Despite these findings, there is evidence in the literature that opioids are efficacious for neuropathic pain; a trial demonstrated that combining gabapentin and morphine for the treatment of neuropathic pain was superior to either alone.[99.] Nonetheless, gabapentinoids may also pose a risk for respiratory depression, drug abuse, and other adverse effects, particularly well established for gabapentin in the postoperative setting.[100,101]

In the form of chronic pain unrelated to nerve injury that does not respond well to other treatments, opioid therapy has been shown to be more effective than placebo or anti-inflammatory medications alone in reducing pain. However, studies have struggled to show substantial improvements in overall functioning with opioid therapy. Although opioids may be effective if used as the sole agent for changing all the primary and secondary effects of chronic pain, they may not be effective enough. The importance of a multi-disciplinary approach to the treatment of chronic pain syndromes cannot be overstated.

The use of opioids requires a comprehensive risk-to-benefit-based strategy, including the consideration of other potentially effective therapies that have less risk. Rational prescription also requires consideration of all potential risks associated with the treatment and should include a plan to avoid or deal with these risks.

Considerations for Opioid Prescribers

In response to a surging public health crisis regarding the misuse of prescription drugs, the Obama Administration in 2011 developed a prescription drug abuse prevention plan through the Office of National Drug Control Policy (ONDCP). The ONDCP plan entails specialized efforts concerning monitoring, proper medication disposal, enforcement, and education. Education of patients, parents, and youth is a key element of focus for the White House-implemented drug misuse prevention plan. Equally important is the education of prescribing physicians and care providers. In 2014, the Federation of State Medical Boards (FSMB) of the United States revised and expanded the book *Responsible Opioid Prescribing: A Clinician's Guide*.[102] The revised guide reviews the new data on opioid risk and toxicity, including high rates of unintended overdose deaths, which were not available when the first edition was written in 2006. It offers clinicians examples of current federal guidelines and strategies to reduce the risk of addiction, abuse, and diversion of opioids. Moreover, the revised edition includes, but is not limited to, defined strategies for patient evaluation that include risk assessment, treatment plans that incorporate functional goals, periodic review and monitoring of patients, documentation, informed consent, and termination strategies for chronic opioid therapy. It also emphasizes the special care that is needed when using methadone and treating children and adolescents, as well as prescriber responsibilities for consumer education on the safe use of opioids. The use of defined risk stratification methods by prescribers of chronic opioid therapy has become paramount. In 2016, the CDC released its *Guideline for Prescribing Opioids for Chronic Pain*, and in 2017, the FSMB published its *Guidelines for the Chronic Use of Opioid Analgesics*. These guidelines offered granular details on the expectations of opioid prescriptions that have been well-received. However, overreactions to the intent of the CDC guidelines resulted in some clinicians leading to rapid and involuntary discontinuation of long-standing opioid prescription, which resulted in increased risks for some patients, including increased illicit drug use and suicide. As a result, the CDC reframed its recommendations in 2019 (see the suggested readings and Chapter 50). However, the risks of chronic opioid therapy, including toxicity, overdose, and OUD, are well-supported by data. However, the benefits of chronic opioid therapy for chronic nonmalignant pain remain weak and inadequate. Therefore the analysis of risks and benefits must shift accordingly and is a critical basis for deciding whether opioids should be initiated. Gourlay and colleagues endorsed a universal precautions approach and suggested that addiction can only be elucidated on a behavioral prospective basis.[103]

Treatment End Points

Pain is a subjective experience, using "pain relief" as a treatment endpoint is a subjective and untestable marker of therapeutic success or failure. One of the most feared consequences of chronic opioid therapy is OUD, which, as discussed earlier, involves compulsive use of an opioid that causes dysfunction and continued use of the opioid despite the dysfunction (i.e. negative impact on or harm to the patient's life). Because effective analgesia should improve function and because of the risk of the side effect of OUD, which hinges on dysfunction, a major focus of chronic opioid therapy should be on functional improvement as an objective endpoint. It is expected that patients who are treated carefully and judiciously with opioids and achieve analgesia should have functional gains. This contrasts with those struggling with an OUD who becomes impaired by substance misuse as manifested by dysfunction. The challenge for physicians treating chronic pain with opioids is to devise a system of objective markers that distinguish function from dysfunction and emphasize a wide spectrum of therapeutic goals.

Several markers of functional improvement can be used in patients chronically treated with opioids. Several standardized

functional measurements (e.g. the 36-item short-form health survey [SF-36] and Oswestry disability index [ODI]) can be used to subjectively measure the reduction in pain with supportive and objective evidence of improvement in functional status and effect on the quality of life. However, psychological and social factors, as well as the status of coexistent disease, may influence the perception of pain, suffering, and entitlement and can alter the overall assessment. Unfortunately, not all of these parameters will improve concomitantly or proportionately following the initiation of opioid therapy. If factors related to psychological and physical reconditioning have not been addressed, pain perception and reduction of pain after a trial of an opioid may be less than optimal.

Determining effective treatment end points during an opioid trial may require flexibility in considering the many possible variations in efficacy and functional gain. A central question that may be useful at the beginning of an opioid trial is, "What do you need to do with this treatment that you cannot do now?" What follows should be the creation of a list of reasonably attainable functional goals that cover multiple domains of the patient's life. Equally important in documenting this list is the process by which the goals will be attained and how the patient plans to document progress toward each functional goal for the clinician on every subsequent follow-up visit, which may include but are not limited to the use of non-opioid pain medicine, physical therapy, acupuncture, injections, and surgery. Each goal was monitored regularly and adjusted based on progress. Expectations may need to be reduced if goals are not met or may be advanced as the patient improves.

One part of determining whether a patient is benefiting from opioid therapy is to gather collateral information from others involved in the patient's care and life. Input from physical and occupational therapists, psychologists, family members, and caregivers may prove invaluable. Evidence of improved function may include gains in employment, increased activities of daily living, and socializing with family and friends. On the contrary, if a patient becomes dysfunctional in employment or social or private life, concerns about possible medication-related deterioration, including addiction, should be raised. However, a decreased function is not pathognomonic of OUD. This may be related to factors other than patient control, such as sedation, cognitive impairment, or other external causes. Suppose these or other external problems are not the cause of a patient's deteriorating mental or physical health. In that case, it may help to consider seeking additional support in the form of a multi-disciplinary program or referral to other specialty providers, such as psychologists, social workers, psychiatrists, or addiction specialists.

It remains controversial whether subjective relief without objective evidence of the improved quality of life is sufficient to justify the chronic use of opioids. Pain reduction is a subjective variable. Its use as an assessment tool for therapeutic success represents only a single aspect of adequate chronic opioid therapy. For example, consider a patient with significant disability related to pain rated six on a pain severity scale of one to ten. Although opioid therapy may not significantly reduce subjective pain scores, this does not signify treatment failure. In fact, despite no reported reduction in pain scores, objective signs of a return to work and increased physical activity clearly demonstrate that treatment has improved the patient's quality of life. Conversely, suppose an opioid trial is characterized by subjective reports of marked pain relief. In that case, there are no observable functional gains and possibly even signs of persistent sedation with decreased physical activity, voluntary unemployment, dysfunctional interpersonal relationships, or diminished physical activity; the physician must consider why the patient would regard this as a positive outcome and attempt to resolve any underlying conditions or misunderstandings.

As noted by the FSMB, a critical aspect of safe opioid management is documentation of a patient's care, including current functional status on initial evaluation and throughout follow up.[104] Documentation not only requires clarity of events but should also offer transparency about the physician's decision process, particularly concerning risk-benefit considerations, choices, and plans for risk management. Vigilance in detecting decreased function is important; this may help reveal problems such as OUD, progressive disease, or pain unresponsive to opioids.

Another critical issue to consider before and during the course of treatment is the discontinuation of opioid therapy if the treatment is deemed ineffective. Many factors must be considered before treatment is considered to be a failure, including inadequate dosing, inappropriate dosing schedule, improper drug delivery route, opioid-insensitive pain, side effects limiting dose escalation, and social and psychological issues.

The appropriate duration of effective opioid therapy remains controversial. Currently, there are no clear guidelines or consensus regarding this issue. The efficacy of treatment, adverse effects of opioid therapy, and progression of the underlying disease must be considered thoroughly when formulating decisions regarding the length of treatment, and these factors must be reconsidered regularly. Once opioid therapy has been initiated, it may be challenging to determine whether pain would be present without opioid therapy unless opioids are tapered.

Key Points

- Opioid drugs have been used to control pain for thousands of years as reliable and potent analgesics, but they do not work for all pain, for everyone, or every condition and may pose serious risks.
- Opioid therapy has undergone intense scrutiny as the opioid crisis, and public health epidemic of excessive prescription drug abuse has been elevated to a national discussion.
- The evidence for sustained benefits of opioids in relieving chronic pain is weak and inadequate, whereas evidence of risk associated with the use of these drugs is clear and substantial.
- Focal attention on the risk-benefit ratio for safe use of opioids underscores the serious potential for opioid abuse and overdose death, which has been well documented through approximately 15 years of retrospective data.
- There is increasing concern about opioid and gabapentinoid related respiratory depression.
- The exact rate of addiction because of prescription opioid use is relatively low but a significant concern.
- Sudden or involuntary discontinuation of opioids may be associated with adverse effects and morbidity.
- Methadone has many features that distinguish it from other opioids, including heightened risk and significant life-threatening adverse outcomes.

- A detailed diagnostic assessment with a thorough history and physical examination, as well as an essential focus on risks and benefits, will drive the selection of specific analgesic treatments.
- The increased risk for abuse and unintentional overdose death requires increased risk management, including risk assessment, treatment plans that incorporate functional goals, periodic review and monitoring of patients, documentation, informed consent, and termination strategies for chronic opioid therapy.
- A thorough history of comorbid psychiatric conditions and a history of substance abuse are important elements of safe prescription.
- Once opioid therapy has been initiated, it may be challenging to determine whether pain would be present without opioid therapy unless opioids are tapered.

Suggested Readings

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49

Minor Analgesics: Non-Opioid and Opioid Formulations

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The use of naturally occurring plant material for the relief of pain dates back to early times. Advances in antipyretic and analgesic medications began in the late 1800s with the development of salicylic acid, antipyrine, phenacetin, and acetaminophen (APAP).[1] These basic medications are still used today to various degrees in both over-the-counter (OTC) and prescription preparations—the minor analgesics salicylic acid and APAP are widely marketed and heavily consumed. Minor analgesics for acute and chronic pain include several prescription and OTC agents, which may be useful in isolation or as adjuvants in a more comprehensive multimodal pharmacologic approach. Many including minor analgesics, OTC medicines include a growing market area for managing acute and chronic pain conditions. Research has demonstrated that at least 80% of adults use OTC medicines as a first response to minor ailments, with great availability of OTCs in the approximately 54,000 pharmacies in the United States and more than 750,000 retail stores that carry these products.[2] A population survey has reported that the use of OTC medications, many of which include minor analgesics, account for the most common method of relieving pain (53%). This is closely followed by physical exercise (52%) and prescription medications (35%).[3]

The minor analgesics reviewed in this chapter include oral APAP, opioid combination preparations (i.e. codeine, propoxyphene, hydrocodone, oxycodone, and tramadol), tapentadol, and buprenorphine products for chronic pain (buccal films and transdermal patch systems), steroids, and caffeine, as well as topical compounds and delivery systems. See the chapters in this text that discuss opioids, anti-convulsants, anti-depressants, and nonsteroidal anti-inflammatory drugs (NSAIDs) for complete information on these topics (Chapters 48, 53, 54, 55, 56, and 57). Additional combination OTC formulations with minor analgesics include convenience combinations—those that contain aspirin, APAP, or ibuprofen plus other remedies such as nasal decongestants, antihistamines, cough suppressants, or antacids. These medications help treat the sequelae of a primary illness (e.g. cold and flu symptoms, insomnia, cough) and any pain symptoms that may coexist.[4]

Prescribing habits regarding the use of analgesics for the treatment of various musculoskeletal conditions continue to evolve. Caudill-Slosberg and colleagues[5] compared prescribing habits between 1980 and 1981 with those between 1999 and 2000 and demonstrated a significant increase in patients receiving prescriptions for acute and chronic musculoskeletal pain. Increases were seen in the use of NSAIDs and cyclooxygenase-2 (COX-2) agents, as well as more potent opioids, including combination opioid preparations containing APAP and NSAIDs.

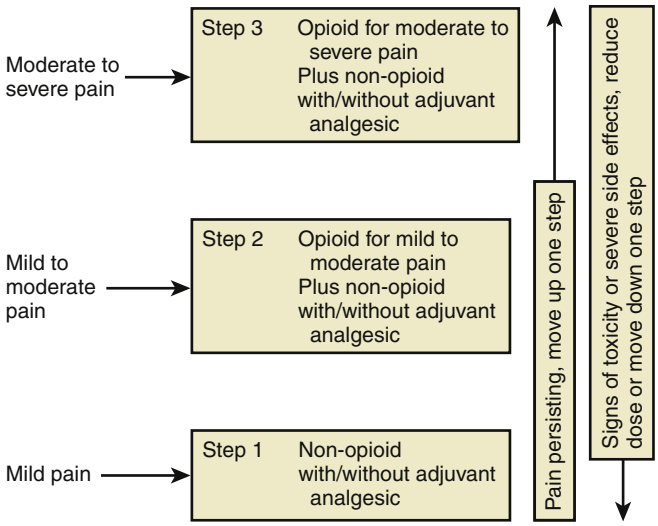
Minor analgesics are used widely, with reported prevalence rates of twice-weekly use of approximately 8.7% for prescription drugs and 8.8% for OTC analgesics. Analgesics are usually the largest selling group of OTC medications in several population studies. Daily use was more common for prescribed analgesics, whereas OTC analgesics were used a few times per week.[6,7] Among prescription and OTC medications, APAP, ibuprofen, and aspirin were the most commonly used (17%–23% of the population).[8] Use of analgesics, many of which include minor agents, accounts for a significant amount of healthcare dollars. In a population study, analgesic cost ranked second behind diagnostic imaging in expenditures for the treatment of acute low back pain.[7] Chronic use of prescription and OTC analgesics (i.e. aspirin, non-aspirin-containing NSAIDs, and APAP) may continue for longer than one year. In the same survey, approximately 2.3 million adults reported using non-aspirin-containing NSAIDs, and 2.6 million used APAP on a frequent basis for longer than five years.[9] This widespread use occurs despite general knowledge of the increased risk for gastrointestinal (GI), renal, and cardiac toxicity with short-term and chronic use. Unfortunately, the perception remains that as a class of medications, OTC and prescription NSAIDs are relatively safe. This misbelief leads to frequent inappropriate use and the potential for serious adverse events.[10] The increased availability and marketing of OTC agents have probably contributed to patient misuse, with consumers still being unaware of the potentially catastrophic risks associated with their use: 60% of people cannot identify the active ingredient in their analgesics, and 40% of Americans believe that OTC drugs are too weak to cause significant harm.[11]

The use of OTC and prescription analgesics is not only confined to the outpatient setting. Significant use of these agents in nursing home facilities was reported in a group of Medicare beneficiaries during 2001. Patients averaged 8.8 unique medications per month, including 2.9 OTC medications. Of these subjects, 70% used non-opioid OTC analgesics and 19.0% used non-opioid prescription analgesics.[12]

Specific Drugs

Minor Opioids

Minor opioids are defined as analgesic combination products with codeine, propoxyphene, hydrocodone, or oxycodone, and dual-mechanism opioid products, including tramadol and tapentadol. Additionally, the chapter will also review buprenorphine



• **Figure 49.1** World Health Organization analgesic ladder. (Adapted from World Health Organization. *Cancer Pain Relief*. Geneva: World Health Organization; 1990.)

formulations for the management of chronic pain, including buccal and transdermal systems or patches. These products continue to account for a large percentage of prescriptions written for chronic and persistent pain conditions. Combination opioid analgesics—compounds containing APAP or anti-inflammatory medications—make up a significant number of opioids prescribed by primary care physicians and pain specialists. Combination analgesics are advocated in several treatment guidelines, including the three-step analgesic ladder of the World Health Organization (WHO) (step 2; Fig. 49.1).[13,14]

Opioid therapy increased dramatically between 1999 and 2010 with a decrease in prescribing in 2013, preceding the Centers for Disease Control and Prevention (CDC) Guideline on prescribing opioids for acute and chronic pain. Within that period, a substitution of opioids for non-opioid analgesics between 2003 and 2006 may have emerged in response to the emerging evidence of cardiovascular risks associated with non-opioid analgesics, primarily NSAIDs.[15] Since the 1990s, the use of minor analgesic combinations containing oxycodone and hydrocodone continued to increase, whereas the use of those containing codeine declined. Clinic type (e.g. primary care, spine center, pain center), geographic, and socioeconomic variables may also affect prescribing practices.[16]

Opioid analgesics as a class can be categorized into three chemical groups: (1) synthetic phenylpiperidines (e.g. meperidine, fentanyl), (2) synthetic pseudopiperidines (e.g. methadone, propoxyphene), and (3) naturally occurring alkaloids derived directly from the poppy seed (e.g. morphine, codeine, thebaine) and their semisynthetic derivatives (e.g. hydromorphone, oxycodone, oxymorphone).[17] This chapter reviews codeine, oxycodone, hydrocodone, and tramadol combination products, as well as formulations of tapentadol and buprenorphine products indicated for the treatment of chronic pain (Tables 49.1 and 49.2).

TABLE 49.1 Minor and Short-Acting Opioids

Class	Name	Adult Dose	Half-Life (Onset)	Mechanism of Action	Other
Natural opium alkaloids	Codeine with acetaminophen (APAP) or acetylsalicylic acid (ASA) (Tylenol No. 2, No. 3, No. 4; Empirin No. 3, No. 4; Capital with Codeine; Aceta with Codeine; Fioricet with Codeine; Fiorinal with Codeine)	PO: 15–60 mg q4h (max daily APAP-ASA dose, 4 g)	2.5–3.5 h (30–60 min)	Opioid agonist activity at multiple receptors—μ (supraspinal analgesia, euphoria), κ (spinal analgesia and sedation), δ (dysphoria, psychotomimetic effects)	Compared with morphine—decreased analgesia, constipation, respiratory distress, sedation, emesis, and physical dependence; increased antitussive effects
Phenanthrene derivatives	Hydrocodone plus ASA or APAP (Lortab, Lortab ASA, Vicodin, Norco, Vicoprofen, ZTuss, P-V-Tussin, Tussafed HC)	PO: 5–10 mg q4–6h (max dose, 4 g)	3.8 h (10–30 min)	Opioid agonist activity at multiple receptors—μ (supraspinal analgesia, euphoria), κ (spinal analgesia and sedation), δ (dysphoria, psychotomimetic effects)	Compared with morphine equivalent analgesia—respiratory depression and physical dependency; equivalent antitussive effects
	Oxycodone (with or without APAP or ASA) (OxyIR, Roxicodone); Oxycodone plus ASA (Percodan, Endodan, Roxiprin); Oxycodone plus APAP (Percocet, Endocet, Tylox, Roxicet, Roxilox)	PO: 5–30 mg q4–6h (4 g max dose of ASA/APAP); sustained-release: 10/10–160 mg q12h	2–5 h (10-15 min)	Opioid agonist activity at multiple receptors: μ (supraspinal analgesia, euphoria), κ (spinal analgesia and sedation), δ (dysphoria, psychotomimetic effects)	Compared with morphine— more potent analgesia, constipation, antitussive effects, respiratory depression, sedation, emesis, and physical dependence
Diphenylheptane derivative	Propoxyphene, with or without APAP (Darvon, Darvon-N); Propoxyphene plus APAP (Darvocet A500, Propacet 100)	PO: 65 mg q4h (max, 390 mg/day); napsylate, 100 mg q4h (max, 600 mg/day)	6–12 h (15–60 min)	Opioid agonist activity at multiple receptors: μ (supraspinal analgesia, euphoria), κ (spinal analgesia and sedation), δ (dysphoria, psychotomimetic effects)	Compared with morphine — less analgesia, sedation, emesis, respiratory depression, and physical dependence

TABLE 49.2 Opioid Combination Products

Drug Class	Drug Name	Trade Name	Available Dose	Typical Dose	Comments	Half-Life
Para-aminophenol derivatives/ natural opium alkaloids	Acetaminophen/ codeine phosphate	Tylenol with Codeine elixir; Tylenol with Codeine No. 2, No. 3, No. 4	(120/12 mg)/5 mL liquid; 300/15 mg, 300/30 mg, 300/60 mg (tablets)	Elixir—children <three years, safe dose not established; three to six years, 5 mL (1 tsp) three to four times daily; seven to 12 years, 10 mL three to four times daily; adults, 15 mL q4h; tablets and capsules, 15–60 mg codeine q4–6h	Codeine phosphate, max, 360 mg daily; acetaminophen, max, 4000 mg daily	Acetaminophen, 1–4 h; codeine, 2.5–3 h
			650/30 mg (tablets)	30–60 mg codeine q4–6h	Codeine phosphate, max, 360 mg daily; acetaminophen, max, 4000 mg daily	Acetaminophen, 1–4 h; codeine, 2.5–3 h
Acetylsalicylic acid/natural opium alkaloids	Aspirin/codeine phosphate	Empirin with Codeine No. 3, No. 4	325/30 mg, 325/60 mg (tablets)	One to two tablets q4h	Codeine phosphate, max, 360 mg daily	Aspirin, 2.5–3.5 h; codeine, 2.5–3 h
Para-aminophenol derivatives/ phenanthrene derivatives	Hydrocodone bitartrate/ acetaminophen	Vicodin, Lorcet-HD, Lortab, Norco, Maxidone, Anexsia	2.5/500 mg, 5/500 mg, 7.5/325 mg, 7.5/500 mg, 7.5/650 mg, 7.5/750 mg, 10/325 mg, 10/500 mg, 10/650 mg, 10/660 mg, 10/750 mg (tablets)	One to two tablets q4–6h	Dosage typically limited by acetaminophen, max, 4000 mg daily	Hydrocodone, 3.5–4.1 h
	Oxycodone/ acetaminophen	Percocet, Endocet, Tylox, Roxicet, Roxilox	5/325 mg, 7.5/325 mg, 5/500 mg (Tylox), 7.5/500 mg, 10/325 mg, 10/650 mg (tablets); 5/500 mg (caplets; Roxicet); 5/325 mg/5 mL (solution) (Roxicet)	One to two tablets q4–6h	Acetaminophen, max, 4000 mg daily	Acetaminophen, 1–4 h; oxycodone, 3.1–3.7 h
Acetylsalicylic acid/phenanthrene derivates	Oxycodone/ aspirin	Percodan, Endodan, Roxiprin	4.8/325 mg (tablet)	One tablet q4–6h	Aspirin, max, 4000 mg daily	Aspirin, 2.5–3.5 h; oxycodone, 3.1–3.7 h
Propionic acid/ phenanthrene derivatives	Hydrocodone bitartrate/ ibuprofen	Vicoprofen	7.5/200 mg (tablet)	One tablet q4–6h	Marketed for short-term management of acute pain; NSAIDs may increase the risk for serious cardiovascular thrombotic events, myocardial infarction, stroke	Hydrocodone, 3.5–4.1 h; ibuprofen, 4–6 h
	Oxycodone/ ibuprofen	Combunox	5/400 mg (tablet)	One to two tablets q4–6h	Max dosage of ibuprofen, 2400–3200 mg daily	Oxycodone, 3.1–3.7 h; ibuprofen, 1.8–2.6 h
Diphenylheptane derivatives	Propoxyphene HC1/APAP		65/650 mg (tablet)	One tablet q4–6h	Structurally related to methadone; propoxyphene HC1, max, 390 mg daily	Propoxyphene, 6–12 h; norpropoxyphene, 30–36 h; acetaminophen, 1–4 h
	Propoxyphene HC1/aspirin/ caffeine	Darvon Compound 65	65/389/32.4 mg (tablet)	One to two tablets q4–6h	Structurally related to methadone; propoxyphene HC1, max, 390 mg daily	Propoxyphene, 6–12 h; norpropoxyphene, 30–36 h; aspirin, 2.5–3.5 h; caffeine, 3–6 h
	Propoxyphene napsylate/ acetaminophen	Darvocet-N 50, Darvocet-N 100, Darvocet A500, Propacet 100	50/325 mg (N 50), 100/650 mg (N 100), 100/500 mg (A500) (tablets)	One to two tablets q4–6h	Structurally related to methadone; propoxyphene napsylate, max, 600 mg daily	Propoxyphene, 6–12 h; norpropoxyphene, 30–36 h; acetaminophen, 1–4 h

NSAIDs, Nonsteroidal anti-inflammatory drugs.

Pharmacokinetics and Pharmacodynamics

Understanding pharmacokinetics and pharmacodynamics is essential for appropriately prescribing minor opioid analgesics, interpreting related toxicology screens, and appreciating the potential mechanisms for adverse side effects. In general, medications are primarily metabolized by the cytochrome P-450 (CYP) and glucuronidation pathways. Opioid analgesics, like any medication, may be metabolized by the CYP drug-metabolizing enzyme system 2D6. Genetic polymorphism of CYP2D6 may lead to variability in enzyme breakdown and clinical effectiveness of the medication. Deficiency of CYP2D6 may be seen in whites (7%) and those of Asian descent (1%).[18] These enzyme systems can be induced (activated) or inhibited by various agents, including drugs, alcohol, and cigarette smoke, as well as by endogenous substances. Inducers are agents that activate the CYP enzyme system and thereby lead to increased metabolism and reduced drug effect. Inhibitors may impair the CYP enzyme system and thus limit the metabolism of the drug and increase the effect of the drug. Although pharmacokinetic drug-drug interactions may affect serum levels of a drug, this may be subclinical in most patients, with significant interactions rarely occurring *in vivo* in only about 10%–15% of patients.[19] Patients' response to individual opioids may vary markedly. Recent evidence has supported more than one mechanism for μ-opioid analgesic reactions, which may be related to receptor polymorphism.[20]

Morphine, hydromorphone, and oxymorphone are not metabolized by CYP but are metabolized by uridine diphosphate glucuronosyltransferase (UGT) enzymes. Except for morphine and codeine, UGT enzymes metabolize medications primarily to inactive metabolites. Morphine is converted into large quantities of relatively inactive morphine-3-glucuronide (M3G) and smaller quantities of the active metabolite morphine-6-glucuronide (M6G). M6G is 50 times more potent than morphine. M3G may account for central nervous system (CNS) toxicity, including lowering of seizure thresholds.[21] Equianalgesic oral doses of the various minor opioid combination products and morphine are listed in Table 49.3.

Codeine

Along with morphine and thebaine, codeine (methylmorphine) is a naturally occurring opium alkaloid derivative. A weak analgesic, codeine is similar in structure to morphine but has an affinity for the μ-opioid receptor 300 times lower. Classically, codeine is thought to be metabolized by *O*-demethylation to its primary active metabolite morphine by the CYP2D6 enzyme.[22] Studies have demonstrated that only a small percentage of the total dose (3%)[23] is converted by CYP2D6 to morphine. Approximately 80% is directly glucuronidated by uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7) enzyme to codeine-6-glucuronide (C6G), an additional active metabolite. The remaining inactive metabolites are primarily norcodeine (2%) and normorphine (2.4%).[24] Nonfunctional CYP2D6 renders codeine ineffective, perhaps because of genetic mutations or deletions[25] or pharmacologic inhibition.[26] Effects of codeine not related to the formation of morphine include cognitive impairment,[27] sedation, dizziness, euphoria and dysphoria, headache, blurred vision,[28] and prolongation of GI transit time. The average half-life of codeine is 2.5 h. Poor metabolizers, based on CYP2D6 genotypes, are present in 7%–10% of the white population and show a decreased metabolism of codeine to morphine and a diminished analgesic effect compared to normal or extensive metabolizers. Ultrarapid metabolism occurring in 1%–7% of the white population versus 3%–10% of Europeans may have an increased formation of morphine and a potential for adverse effects at recommended doses of codeine.[29] Because of the unpredictable metabolism of codeine as an analgesic, codeine is often replaced by other opioids or combination products.

Efficacy

When used alone, codeine is typically prescribed in doses of 30–60 mg every 4–6 h, with the onset of analgesia taking place in 30–60 min and the duration of effect lasting 4–6 h. Codeine has been shown to be an effective cough suppressant (10–120 mg/day) and is present in several OTC cold and cough convenience preparations.[30] However, codeine's potential opioid analgesic effect has long been questioned. Houde's classic study in the 1960s reported the analgesic effects of codeine (32 mg) to be no more than that of 650 mg of aspirin, although both were more effective than placebo.[31] The number needed to treat (NNT), or the number of patients needed to receive the medication to achieve at least 50% pain relief, with 60 mg codeine, has been reported to be 16.7,[32] which has led to its widespread use as a combination analgesic.

TABLE 49.3 Combination Analgesics for Mild to Moderate Pain

Agent	Onset (min)	Duration of Action (h)	Equianalgesic Oral Dose (mg)*	DEA Schedule
Oxycodone combinations	10–15	4–6	30†	II
Hydrocodone combinations	30–60	4–6	30	III
Codeine combinations	30–60	4–6	130	III
Propoxyphene combinations	15–60	4–6	130	IV
Tramadol combinations	60	6–7	100	III

DEA, United States Drug Enforcement Agency.

*Doses reflect the opioid component only and are equianalgesic to 30 mg morphine.

†Doses for moderate to severe pain not necessarily equivalent to 30 mg morphine.

From Gutstein HB, Akil H. Opioid analgesics. In: JG Hardman, LE Limbird, AG Gilman (eds). *Goodman and Gilman's the Pharmacological Basis of Therapeutics,*. 10th ed. New York: McGraw-Hill; 2001: 569–619.

Codeine (10–60 mg) is more commonly prescribed in combination with APAP (400–1000 mg), aspirin, or NSAIDs such as ibuprofen (400 mg). A systematic review of codeine and APAP trials for acute non-cancer-related pain concluded that the benefit over codeine alone is only modest (5%).[33] A systematic review of trials of APAP alone or in combination with codeine noted efficacy in patients prescribed APAP plus 60 mg codeine versus APAP alone. At doses higher than 60 mg, incremental analgesia was diminishing with increasing doses and a higher incidence of side effects (e.g. constipation, nausea, and sedation).[34] A head-to-head study of codeine (30 mg) plus APAP (300 mg) and hydrocodone (7.5 mg) plus APAP (500 mg) showed significant relief of moderate to severe acute (6 h) postoperative pain than placebo, but the analgesia was no greater than that achieved with hydrocodone-APAP.[35]

Propoxyphene (Dextropropoxyphene)

Propoxyphene (dextropropoxyphene) is a mild synthetic opioid originally synthesized in the 1950s and at one point marketed in its hydrochloride form as Darvon (65 mg; maximum, 400 mg/day), as propoxyphene napsylate (Darvocet-N 50, Darvocet-N 100), and in Europe, as co-proxamol (32.5 mg dextropropoxyphene plus 325 mg paracetamol). By the late 1960s, propoxyphene was the most widely prescribed analgesic in the United States.[36] Reports of propoxyphene overdoses led to warnings by the United States Food and Drug Administration (FDA) in 1978 and a subsequent reduction in use.[37] Propoxyphene's major metabolite norpropoxyphene has fewer CNS effects than propoxyphene does but accumulates in cardiac tissue, thereby leading to a local anesthetic effect and prolongation of action potentials, in some cases fatal torsades de pointes.[38] Because of the increasing number of fatal overdoses of co-proxamol and limited evidence supporting its efficacy versus APAP for acute and chronic pain, the British government announced the gradual withdrawal of co-proxamol from British markets in January 2005.[39] As a result of increasing public outcry from patient advocacy groups and recommendations by an FDA advisory board group, propoxyphene was voluntarily removed from the United States market in 2011 and India in 2013.[40,41] It is interesting to note that at the time of its withdrawal from the market, a survey showed that 68% of pain medicine practitioners saw patients who were prescribed propoxyphene by their primary care physicians.[42] Propoxyphene is still allowed in some countries, although with prescription.

Oxycodone

Oxycodone is a semisynthetic opioid analgesic derived from the opium alkaloid thebaine. Human studies have demonstrated it to have analgesic potency 1.5 times that of morphine after oral administration.[43] Several active metabolites have been proposed to contribute to the clinical pharmacokinetics of oxycodone. One theory supports 3-*O*-demethylation by CYP2D6 to oxymorphone. Oxymorphone is a potent μ-opioid ligand with two to five times higher receptor affinity than morphine has. Though potent, oxymorphone accounts for only 10% of oxycodone metabolites. Oxymorphone has been available for several years for parenteral and rectal use and was reformulated and released in an immediate-release (IR) and extended-release (ER) schedule II formulation. *In vitro* studies have shown that *O*-demethylation of oxycodone accounts for 13% of its oxidative metabolism. Oxidation of oxycodone primarily occurs via *N*-demethylation by CYP3A4/5 to noroxycodone, which is the most abundant circulating metabolite in human studies. Unfortunately, noroxycodone has a weak affinity for μ-opioid receptors.[44]

In vivo, oxycodone has potent μ-opioid receptor effects, but data suggest that the intrinsic antinociceptive effects may be additionally mediated by κ-opioid receptors.[45] This has led some to consider oxycodone an ideal medication for opioid rotation in patients not responsive to morphine, a classic μ-opioid receptor agonist.[46,47] Recent studies have proposed non-CYP2D6 metabolites (noroxycodone, noroxymorphone, noroxycodols, oxycodols) as additional substances responsible for its μ-opioid receptor binding and analgesic effects.[48] Animal studies have recently demonstrated conflicting gender-related differences in female versus male rats when examining the antinociceptive effects of oxycodone.[49]

Hydrocodone

Hydrocodone is similar in structure to codeine but is six to eight times more potent.[50] Hydrocodone is a prodrug and undergoes CYP2D6 metabolism to hydromorphone and CYP3A4 metabolism to noroxycodone. Hydrocodone is less potent than morphine by receptor affinity and demonstrates a relative analgesic potency of 0.59 compared to morphine. The discrepancy between hydrocodone's binding affinity and potency versus that of morphine is possibly the result of active hydrocodone metabolites or the intrinsic efficacy of receptor activation, which is more efficient for hydrocodone than for morphine.[51] Hydrocodone is marketed as a combination product with APAP, ibuprofen, and aspirin (HCPs).

Efficacy

The hydrocodone-ibuprofen combination product was introduced in the United States in 1997 as a fixed dose of hydrocodone (7.5 mg) and ibuprofen (200 mg) and has demonstrated efficacy for acute postoperative pain.[52] Neither hydrocodone (7.5 mg) nor ibuprofen (200 mg) given alone was superior to placebo, thus supporting the concept of analgesic synergy between the two agents. Similar findings were demonstrated in patients with acute low back pain,[53] and postoperative obstetric and gynecologic pain.[54] Hydrocodone-APAP (7.5, 200 mg), one and two tablets, compared to a fixed dose combination of codeine (30 mg) and APAP (300 mg). The two tablet dose of combination hydrocodone-APAP was more effective than the one tablet dose and one or two tablets of the fixed codeine-APAP combination.[55]

In 2014, to counter the increasing prevalence of opioid misuse, over-prescribing, and growing number of overdose deaths, the Drug Enforcement Agency (DEA) rescheduled hydrocodone combination products from DEA Schedule III to DEA Schedule II, leading to a reduction in prescribing of HCPs for acute and chronic pain, with a subsequent increase in other minor opioids including codeine-containing products and tramadol.[56-58] Commonly prescribed hydrocodone-APAP combination products presently include 10, 7.5, and 5 mg hydrocodone and 325, 500, 750 mg APAP, with ranges between 5 and 10 mg hydrocodone and 325 and 750 mg APAP (Hydrocodone Bitartrate/Acetaminophen Tablets, package insert, Mallinckrodt, Inc., St. Louis).

Long-acting and extended-release hydrocodone formulations entered the United States market in 2013 and include an ER hydrocodone product (hydrocodone bitartrate ER capsules [Zohydro], Zogenix, Inc., San Diego.), followed in 2014 by approval of hydrocodone bitartrate (Hysingla ER) [Purdue Pharma] (Hysingla ER [package insert]. Stamford, CT: Purdue Pharma LP, February 2015), a once-daily formulation. Both formulations are categorized with abuse deterrent properties and are indicated for pain severe enough to require around-the-clock, long-term treatment and for which alternative treatment options are inadequate. The two ER

hydrocodone products also include drug interaction warnings related to possible cytochrome P450 interactions, including the role of CYP3A4 isoenzymes impacting hydrocodone clearance. CYP3A4 inhibitors, such as ketoconazole, macrolide antibiotics, and protease inhibitors (e.g. ritonavir), may cause increased levels of hydrocodone because of a decrease in drug clearance. CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may lead to a lack of efficacy or withdrawal syndrome in patients with physical dependence on hydrocodone. A third ER hydrocodone product, hydrocodone bitartrate (Vantrela ER, Teva) (Vantrela ER, Hydrocodone Bitartrate PI, Teva, 2017) was approved in 2017 with abuse deterrent technologies to reduce the risk of oral, intranasal, and intravenous abuse via manipulation of the tablets, but is currently not available.

Tapentadol

Tapentadol, 3-((1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl) phenol hydrochloride, is a non-racemic molecule used to treat moderate degrees of chronic or central pain syndromes.[59] Tapentadol (Nucynta) was approved in 2008 (Nucynta PI, Ortho-McNeil-Janssen Pharmaceuticals, 2008) and is available in 50, 75, and 100 mg doses. An extended-release formulation, tapentadol ER, was approved in 2011 for chronic pain uniquely for the management of neuropathic pain associated with diabetic peripheral neuropathy with recommended dosing BID (50 mg, 100 mg, 150 mg, 200 mg, and 250 mg strengths) (Nucynta ER PI, Janssen Pharmaceuticals, Inc, Titusville, NJ, 2014).

Tapentadol has a dual action with both opioid and neuropathic properties, given it is opioid receptor affinity and monoamine reuptake inhibition and is considered a strong synthetic opioid. In clinical trials, tapentadol has been shown to have higher tolerability and comparable efficacy to oxycodone. Tapentadol is a μ-opioid receptor agonist and a norepinephrine reuptake inhibitor.[60] It also possesses serotonin reuptake inhibitor properties; however, not enough to contribute significantly to its analgesic profile. It binds to the μ-opioid receptor selectively, and its affinity is 44-fold lower than morphine.[57] Despite this lower affinity, tapentadol is only two to three times less potent than morphine as an analgesic. This is mainly because of the dual-analgesic mechanisms of action. Tapentadol's neuropathic properties increase levels of norepinephrine which leads to analgesia through activation of inhibitory alpha-2 receptors. Its mechanism of action on the μ-opioid receptor and norepinephrine reuptake both independently and synergistically contribute to the analgesic effect. However, this synergistic quality is not evident in the drug's side effect profile.[61] Thus with a lesser adverse effect profile than typical opioid medication, tapentadol has higher tolerability. Tapentadol is available as IR and ER formulations. Regarding the conversion of tapentadol IR to ER, a direct milligram to milligram conversion on a total daily dose basis is appropriate.

Tapentadol has an oral bioavailability of 32% because of first pass metabolism. When taken orally, the medication is absorbed rapidly and reaches a plasma steady-state concentration in approximately 25–30 h when taken regularly. Close to 97% of the drug is metabolized to inactive metabolites by glucuronic acid significantly and to a lesser degree by CYP enzymes. Once metabolized, the resultant molecule does not have analgesic properties. All metabolites and parent compounds are renally excreted.

Buprenorphine

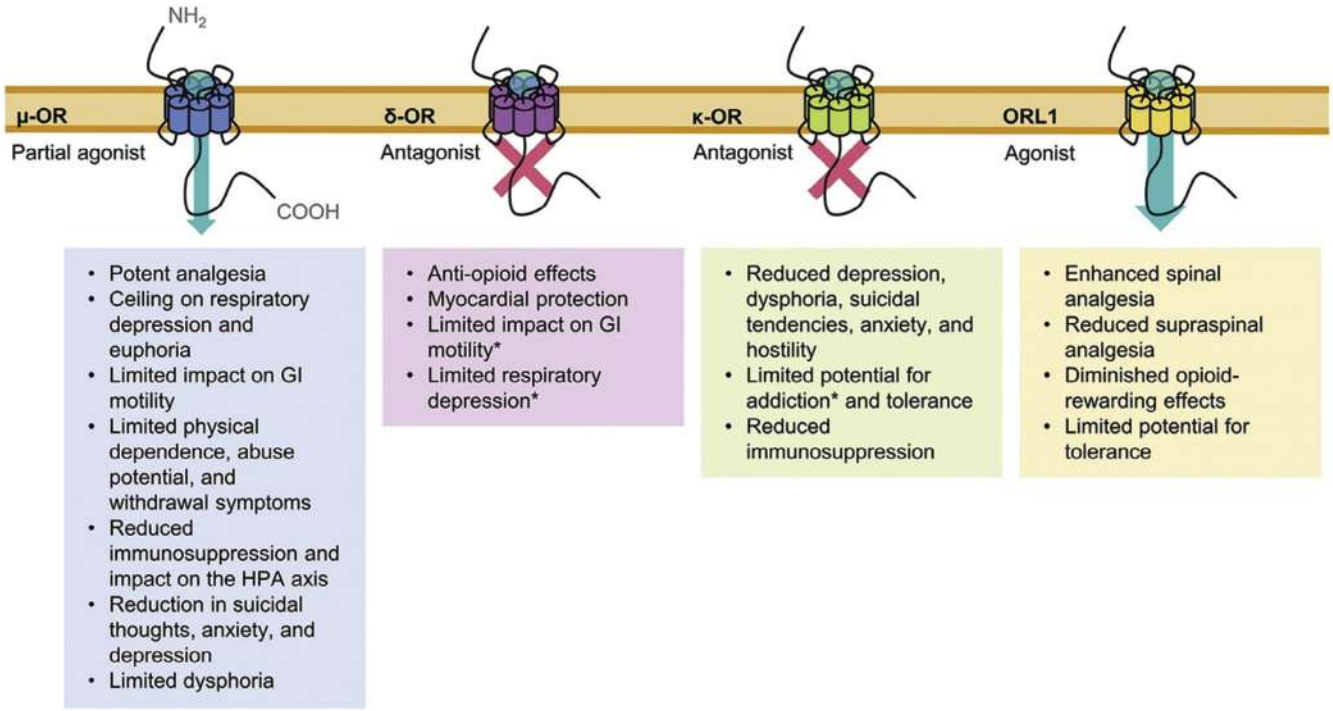
Buprenorphine is a schedule III lipophilic semisynthetic derivative of thebaine and possesses unique opioid activity compared to traditional opioids, including partial μ-opioid agonist and multiple nonselective mixed agonist-antagonist opioid receptor activity (κ-opioid, δ-opioid), opioid receptor-like 1 [ORL1]). Buprenorphine's unique characteristics as an opioid include a bell-shaped analgesic dose-response curve related to unique binding affinity,[62] and ceiling effect for respiratory depression, making it an attractive option for clinical settings because of reduced potential for toxicity and overdose.[63] The FDA indications for the use of buprenorphine include opioid detoxification, opioid maintenance treatment, and management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.[64]

Buprenorphine has multiple agonist-antagonist properties. It is a partial agonist of the μ-opioid receptor, with high binding affinity and slower dissociation from the μ-opioid receptor, which may contribute to prolonged analgesia and less potential for withdrawal.[65] It is an antagonist of the κ-opioid and an agonist at δ-opioid receptors and also shows to have weak affinity for the ORL-1 receptor, an opioid subfamily of G protein-coupled receptors. It also possesses a strong local anesthetic effect, given that it also blocks voltage-gated sodium channels. See Figure 49.2 for a description of the unique pharmacodynamic properties of buprenorphine related to opioid receptor multi-mechanistic activity that may result in enhanced analgesia and decreased side effects.[66]

Buprenorphine is hepatically metabolized via the CYP3A4 enzyme into norbuprenorphine and undergoes glucuronidation by UGT1A1 and UGT2B7 before being eliminated through bile excretion. The compound is thus relatively safe in those with renal compromise. Although possessing a higher degree of respiratory depression properties, the metabolite norbuprenorphine does not pass the blood–brain barrier easily and thus does not exact this side effect to the same degree as other opioid compounds. Nevertheless, respiratory depression can still be a factor to monitor.

Buprenorphine formulations include intravenous, sublingual, buccal, and transdermal systems (patch). There are two sublingual/buccal formulations of buprenorphine indicated for maintenance treatment of opioid dependence and during induction. One formulation of sublingual buprenorphine (Subutex Package Insert, Indivior UK Ltd., 2018)), available in 2 mg and 8 mg pills, is indicated for opioid dependence and is preferred for initiation of treatment. Suboxone is a combination product of buprenorphine and naloxone (Suboxone Package Insert, Indivior, Inc, 2018), formulated in a 4:1 ratio of buprenorphine to naloxone, is indicated for maintenance treatment of opioid dependence (2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg, 12 mg/3 mg). Naloxone is an opioid receptor antagonist, and its addition is meant to deter abuse by crushing, which could precipitate severe opioid withdrawal.

Two buprenorphine formulations FDA approved for chronic pain include a buccal film (Belbuca) and transdermal patch (Butrans). Buprenorphine buccal film (Belbuca, Endo Pharmaceuticals, Inc, 2015) is a schedule III opioid long-acting medication indicated for chronic pain (the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate). Conversion to the buccal film from other opioids includes for those patients opioid naïve or on <30 morphine equivalent doses (MED) start at 75 mcg film every 12 h; 30–89 MED, 150 mcg every 12 h; and 90–160 MED, 300 mcg every 12 h. Incremental titrations should not be done more frequently than every four days. This medication is not indicated for patients currently on >160 MED. The dissolvable film is placed against inside the check, holding for 5 s, to allow the film to stick, and usually dissolves within 30 min. Buprenorphine buccal film includes a range of doses (75, 150, 300, 450, 600,



• **Figure 49.2** Pharmacodynamic properties of buprenorphine: multi-mechanistic regulation of opioid receptors (Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain. *Pain Ther.* 2020;9:41–54.)

750, and 900 mcg). Patients being converted from other opioids should have their MED decreased to less than 30 MED prior to initiating therapy.[67]

Buprenorphine formulated in a transdermal system or patch (Butrans Package Insert, Purdue Pharma LP 2019) provides lower serum blood levels compared to oral formulations and is indicated for chronic pain in opioid naïve and patients on relatively lower MED. This formulation is not indicated for opioid use disorder, maintenance, or detoxification.

Buprenorphine transdermal patch system (Butrans Package Insert, Purdue Pharma, 2019) provides continuous systemic delivery of buprenorphine for seven days. Dosage strengths include 5, 7.5, 10, 15, and 20 mcg/h patch systems. The product is also FDA approved for the management of pain severe enough to require around-the-clock, long-term opioid treatment and has demonstrated efficacy in chronic osteoarthritis pain and chronic low back pain.[68,69] For opioid naïve patients, treatment is initiated at 5 mcg/h every seven days, with dose titrating to the next higher level after a minimum of 72 h. When converting patients taking other opioids to a buprenorphine patch system, it is recommended to taper the patient's current opioids for up to seven days to no more than 30 mg of MED before initiating therapy at 5 mcg/h for seven days. Patients on 30–80 MED can be converted with the initiation of a 10 mcg/h patch. In the United States, the maximum buprenorphine transdermal system dose is 20 mcg/h because of a potential risk of QTc interval prolongation, which was noted in clinical trials used to obtain FDA approval. Patients are advised to avoid exposing the patch site to direct external heat sources while wearing the patch because of the potential dose-dependent increase in buprenorphine release and possible opioid toxicity and overdose. The most common adverse events reported in clinical trials included nausea, dizziness, headache, and application site pruritus (Butrans Package Insert, Purdue Pharma LP 2019).

Acetaminophen

APAP (paracetamol) and APAP combination products (i.e. containing opioids) are commonly prescribed as a minor analgesic for acute and chronic pain (Table 49.2). The 2000 American College of Rheumatology and similar European professional colleges have recommended it as first line pharmacologic therapy for osteoarthritis (OA).[70,71] Prescription APAP is available as an opioid-containing combination product (e.g. codeine, hydrocodone, oxycodone), whereas OTC preparations may be combined with pseudoephedrine or dextromethorphan as convenience drugs.

Mechanism of Action and Description

APAP (paracetamol) is a *p*-aminophenol analgesic that was introduced in the late 1800s in Germany, a product of the rapidly developing chemical industry. Newly synthesized compounds included synthetic antipyretics and analgesics such as acetophenetidin (phenacetin), antipyrine (phenazone), and acetylsalicylic acid (ASA; aspirin).[72] Paracetamol, the active metabolite of phenacetin, was found to demonstrate less intense GI side effects, which led to its use as an analgesic. Paracetamol was formally introduced in the United States in the 1950s, and although it was found in the 1960s to have hepatotoxic effects with unintentional misuse and overdose, it became one of the most widely used OTC and combination prescription analgesics worldwide.

The pharmacologic mechanism of action of paracetamol remains unclear. Generally, it has known analgesic and antipyretic activity with no known peripheral anti-inflammatory or platelet effects. Its antipyretic activity may be secondary to blockade of prostaglandin (PG) production and inhibition of PG endoperoxide H_2 synthase and COX centrally. APAP may block COX activity by reducing the active form of COX to an inactive form, but with only limited effects in the GI tract and peripherally at sites of

inflammation, thus contributing to a lower GI side effect profile than that of NSAIDs.[73] Further, recent studies have suggested that its central analgesic qualities may be related to decreased activation of a subtype of endogenous opioid peptide, β-endorphin.[74]

APAP is available in oral and rectal formulations and is rapidly absorbed from the GI tract, mainly the small intestine.[75] APAP has a half-life ($t_{½}$) of between 1.25 and 3 h and therapeutic serum levels of 10–30 μg/mL. Twenty-five percent of the dose undergoes first pass metabolism in the liver. Up to 90% of APAP is metabolized in the liver via glucuronidation and sulfate conjugation to nontoxic metabolites. The remaining 10% undergoes oxidative metabolism via the CYP system (CYP-450 2E1 and CYP-450 1A2), which is responsible for the formation of the potentially hepatotoxic and nephrotoxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI; Fig. 49.3). This minor pathway becomes more critical when the enzyme system responsible for sulfonation and glucuronidation becomes saturated with doses higher than 150 mg/kg, thereby increasing the total fraction of NAPQI. Approximately 85% of the dose is excreted in urine within 24 h of oral dosing. NAPQI is itself detoxified by conjugation with glutathione.[76] Case reports have suggested that clinical situations characterized by low glutathione levels (e.g. chronic hepatitis C, malnourishment, human immunodeficiency virus infection, cirrhosis) may place these patients at greater risk for adverse events from APAP. However, one study found no significant evidence that these populations are at higher risk for APAP toxicity.[77] There are few clinically significant pharmacokinetic interactions with therapeutic doses of APAP. Although case reports have attributed an elevated international normalized ratio (INR) to APAP and oral anticoagulant drug interactions,[78] randomized controlled studies have found no evidence of clinically significant changes in the INR.[79] Even though studies have demonstrated an association, there is no clear evidence of cause and effect.[80]

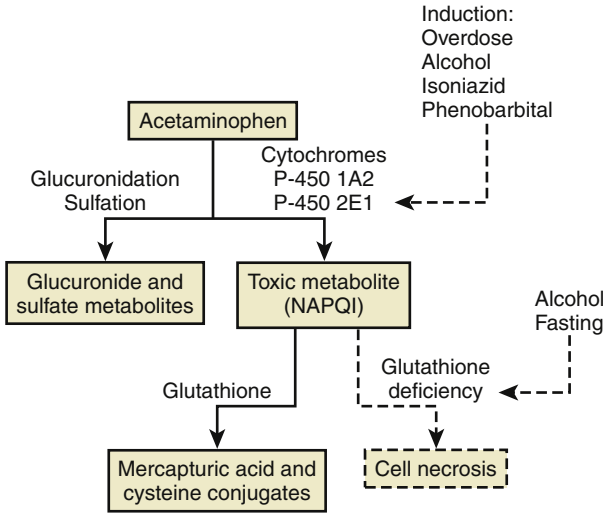
Risks and Precautions

APAP-induced toxicity is often associated with liver and renal dysfunction. APAP hypersensitivity reactions are rare, but severe reactions are possible. In general, chronic administration of APAP may cause depletion of glutathione stores and hence lead to greater production of the hepatotoxic and nephrotoxic metabolite NAPQI. Current recommendations for a maximum daily dosage of APAP are approximately 4 g/day in adults and 75 mg/kg/day in infants and children (Box 49.1).[81] Unintentional liver injury, such as hepatic necrosis or acute liver failure from self-medication with OTC and prescription APAP products, can develop with dosages exceeding 4 g/day.

The serum alanine transaminase (ALT) level may be elevated with the acute use of recommended doses of APAP. Watkins and Seeff[82] studied healthy adults given 4 g of APAP for 14 days. They found that 31%–44% of the study subjects, including patients taking APAP and various opioid-APAP combination products, demonstrated elevations to three times the upper limit of normal (typically considered clinically significant). Opioids were found to have no additional effect on ALT levels. Elevated liver function is not routinely seen with chronic use and is thought to occur because of cellular adaptation.[82] This APAP tolerance may be characterized by possible downregulation of CYP bioactivation and increased glutathione production by liver hepatocytes.[83]

The concomitant use of alcohol and APAP resulting in increased risk, lower threshold for hepatic and renal toxicity, or both remain controversial and reported primarily in retrospective reviews and case reports.[84] Acute and chronic alcohol use contribute to drug-induced hepatotoxicity via induction of CYP2E1 and NAPQI formation.[85] Enhanced ethanol-related toxicity was demonstrated only in patients at high risk with APAP levels above 300 mg/mL, a level far above the package insert recommendation for no more than three alcoholic beverages daily.[86] When consumed with APAP, ethanol may block the formation of NAPQI.[87] Other inducers of hepatic isoenzymes CYP2E1 and CYP1A2 that are commonly used for pain management include carbamazepine, oxcarbazepine, barbiturates, and phenytoin (Box 49.2).[88] Most importantly, the risk for APAP-induced hepatotoxicity may be increased in patients with alcoholic hepatic disease, viral hepatitis, or alcoholism because of a reduction in glucuronide conjugation and subsequent depletion of glutathione reserves.

Chronic APAP prescribing should be avoided in patients with renal disease, although the exact mechanism of injury is unknown



• **Figure 49.3** Metabolism of acetaminophen. NAPQI, *N*-acetyl-*p*-benzoquinoneimine. (From Barkin RL. Acetaminophen, aspirin, or ibuprofen in combination analgesic products. *Am J Ther.* 2001;8:433-442.)

• Box 49.1 Acetaminophen Dosing Considerations

Dosing for Mild Pain

- 325–1000 mg PO, per rectum, q4–6h
- Maximum dose: 1 g/dose; 4 g/24 h
- American Liver Foundation: patients should not exceed 3 g/day for any prolonged period*

Renal Impairment

- Adjust dose frequency
- Creatine clearance (CrCl) = 10–50 mL/min, q6h; CrCl <10 mL/min, q8h

Hepatic Impairment

- Use with caution
- Consider decreasing the dose, monitor liver function, avoid chronic use

Counseling Patients

Acetaminophen (APAP) in over-the-counter products:

- Regular strength APAP products commonly contain 325 mg/tablet
- Extra strength APAP products commonly contain 500 mg/tablet

*Based on a study by Watkins and Seef.[82]

• Box 49.2 Agents That Increase Risk for Acetaminophen Hepatotoxicity Through Cytochrome P-450 (CYP) Induction

- CYP1A2
  - Barbiturates
  - Bupropion (possible)
  - Caffeine
  - Carbamazepine
  - Charcoal-broiled food
  - Cruciferous vegetables
  - Dihydralazine
  - Isoniazid
  - Phenytoin
  - Primidone
  - Rifampin
  - Ritonavir
  - Sulfinpyrazone
- CYP2E1
  - Ethanol
  - Isoniazid

Adapted from Barkin RL. Acetaminophen, aspirin, or ibuprofen in combination analgesic products. Am J Ther. 2001;8:433-442.

and may be relevant only in patients with preexisting renal compromise or systemic disease.[89] Patients with a history of salicylate hypersensitivity characterized by drug-induced urticaria have demonstrated 11% cross-reactivity to APAP.[90] APAP use has been shown to be associated with hypertension in two large prospective studies in women.[91,92] Similar studies in healthy men failed to show an association between the use of APAP and hypertension.[93] Analgesics, in general, may modestly affect blood pressure via several mechanisms, primarily through the kidney or systemic COX-2 inhibition of PGs, which leads to an imbalance between the vasodilators PGI_2 and PGE_2 and the vasoconstrictors $PGF_2\alpha$ and thromboxane A_2. These effects on PG synthesis are greater with NSAIDs than with APAP.[94]

Clinical Use

Although several guidelines traditionally recommended APAP as a first line agent, its advantages over NSAIDs in managing OA-related pain remain controversial. A double-blind trial of paracetamol, 4 g/day, for one month found it to be as effective as both analgesic and anti-inflammatory doses of ibuprofen in patients with knee OA.[95] The 2019 American College of Rheumatology (ACR) guideline for hand, hip, and knee osteoarthritis conditionally recommended acetaminophen for patients with knee, hip, and/or hand OA.[96] A "conditional recommendation" is given when the quality of evidence is low or very low and/or the balance of benefits versus harms and burdens was sufficiently close that shared decision making press between the patient and clinician is necessary. This recommendation was based on clinical trials where the effect sizes are small, and meta-analysis suggests that APAP as monotherapy may be ineffective.[97] The latest ACR osteoarthritis guideline recommended APAP consideration for those with limited medication options because of intolerance or contraindications to the use of NSAIDs for short-term or episodic use.[96]

Studies have demonstrated the efficacy of both a traditional NSAID (diclofenac)[98] and a COX-2 inhibitor (celecoxib)[99] versus APAP in hip and knee OA cohorts. A Cochrane database review of the use of APAP for the chronic pain of OA found the drug to be less effective than NSAIDs in terms of pain reduction scores, although the superiority of NSAIDs over APAP appeared to be more evident in OA patients with more severe pain. Both the NSAID and APAP groups had similar efficacy concerning functional status.[100] APAP may retain anti-inflammatory action comparable to that of NSAIDs in patients with knee OA. Brandt and associates[101] performed a pilot study of 30 subjects in whom OA of the knee was diagnosed and showed that treatment with APAP results in similar significant decreases in mean total knee effusion volume (measured by magnetic resonance imaging) as does treatment with NSAIDs. A systematic review on the efficacy of acetaminophen for chronic pain demonstrated no or little efficacy for the treatment of chronic pain conditions and recommended assessment of continuous efficacy with patient use.[102]

Tramadol

Tramadol, (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is a synthetic racemic mixture typically used for its centrally acting analgesic properties. Clinical and basic science studies have described numerous mechanisms of action at central and peripheral sites. Tramadol is classified as a weak synthetic opioid with mild serotonin and norepinephrine reuptake-inhibiting effects.[103]

Mechanism of Action and Description

The most well-studied mechanism of action of tramadol is its weak affinity for opioid receptors, the most significant of which involves the μ receptor. Tramadol-induced analgesia is only partially inhibited by the opiate antagonist naloxone, thus suggesting additional non-opioid-related analgesic mechanisms.[104] Tramadol also displays an inhibitory effect on the central neuronal norepinephrine and serotonin (5-HT) reuptake systems. Additional actions include a local anesthetic effect, anti-inflammatory effects in experimental rat models, and reduction of substance P levels in human synovial fluid.[105,106] Although α_2-agonist activity has also been reported, concentrations in the range of 10–100 μmol/L do not bind significantly to α_2-adrenergic receptors.

Tramadol's affinity for the μ receptor appears to be approximately ten times weaker than that of codeine, 60 times weaker than that of dextropropoxyphene, and 6000 times weaker than morphine (Table 49.4).[104] The active *O*-demethylated metabolite

TABLE 49.4 Affinity of Tramadol and Selected Compounds for Opioid Receptors

	K_i VALUES (mmol/L)		
Drug	μ Receptor	δ Receptor	κ Receptor
Morphine	0.00034	0.092	0.66
Dextropropoxyphene	0.034	0.38	1.22
Codeine	0.2	5.1	6.0
Tramadol	2.1	57.6	42.7
Imipramine	3.7	12.7	1.8

Note: lower K_i = higher binding affinity. K_i, constant of inhibition.

From Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittelforschung.* 1988;38:877-880.

M1 has 300 times higher affinity for the μ receptor than the parent compound does and is up to six times more potent in producing analgesia.[107]

Central Neuronal Actions

Multiple actions affecting the descending inhibitory pain pathways have been reported.[108,109] The first system involves neurons originating in the periaqueductal gray matter in the midbrain that synapse at the nucleus raphe magnus, from which fibers then project to the spinal cord. Inhibition of 5-HT reuptake may contribute to inhibition of pain. Another pathway originates at the locus coeruleus in the pons, with fibers projecting to the spinal cord. The norepinephrine released from this pathway inhibits pain responses at the spinal cord via an α-adrenergic mechanism.

Activation of these descending pain inhibition pathways stimulates interneurons that inhibit the transmission of painful stimuli in the dorsal horn by the action of endogenous opioids. Opioid receptor activity has been proposed to be mediated by the dextrorotatory (+) enantiomer instead of the levorotatory (–) enantiomer.[110] The (–) enantiomer is approximately ten times more potent than its (+) counterpart in the inhibition of norepinephrine uptake, and the (+) enantiomer is approximately four times more potent than the (–) enantiomer in the inhibition of 5-HT uptake. M1 retains a higher affinity for the μ-opioid receptor (300–400 times) and possesses greater analgesic activity than the parent compound does. The M1 (+) enantiomer acts at the μ receptor, whereas the M1 (–) enantiomer mainly inhibits the reuptake of norepinephrine (Table 49.5).[108,109]

Formulations include IR and sustained-release (SR) oral forms (SR, dosing every 12 h; ER, dosing every 24 h); injectable solutions for subcutaneous, intravenous, or intramuscular administration; and a rectal formulation. SR formulations are available in several countries worldwide, but only the ER formulation is currently available in the United States. In addition, an orally disintegrating tablet version of tramadol (Ralivia FlashDose) for the treatment of moderate to moderately severe pain is under development.[111] Tramadol is currently recommended for the treatment of moderate to moderately severe pain in patients unresponsive to previous oral therapies or who have a contraindication to COX-2-selective or COX-2-nonselective NSAIDs.

History

Tramadol has been available in Germany since 1977, where it remains one of the most widely prescribed analgesics. Before its United States release in 1995, clinical[112] and epidemiologic studies[113] suggested that tramadol demonstrates low abuse potential, which led the Drug Abuse Advisory Committee to recommend FDA approval of tramadol as a nonscheduled analgesic. Current studies continue to support the low abuse potential of tramadol. A post-marketing survey has demonstrated limited evidence of tramadol use-related dependence, withdrawal, and abuse.[114] Another study assessing the prevalence of abuse compared tramadol with NSAIDs and hydrocodone-containing analgesics in patients with chronic non-cancer-related pain.[115] This study used an abuse index that identified subjects according to the following behavior: (1) increased doses without physician approval, (2) used for purposes other than intended, (3) demonstrated an inability to stop use, and (4) experienced withdrawal. The percentage of subjects who scored positive (at least one of the four types of behavior) during 12 months was 2.5% for NSAIDs, 2.7% for tramadol, and 4.9% for hydrocodone.

Formulations

Currently available oral formulations of tramadol include 50 mg scored IR tablets, SR tablets and capsules (every 12 h dosing available worldwide but not in the United States), two ER once-daily tablets (Ultram ER and Ryzolt [Purdue Pharma]), and combination tablets consisting of tramadol, 37.5 mg, plus APAP, 325 mg.[116] The SR preparations are available in strengths of 50, 100, 150, and 200 mg taken twice daily. ER tramadol hydrochloride tablets (Ultram ER) are available in 100, 200, and 300 mg strengths taken once-daily. The bioavailability of Ultram ER, 200 mg, relative to tramadol, 50 mg IR formulation every 6 h, is approximately 85%–90%. Steady-state plasma concentrations of tramadol and M1 are achieved within four days of once-daily dosing. Important pharmacokinetic parameters of the 200 mg ER formulation include a time of maximum concentration (T_{max}) of 12 and 15 h for tramadol and the M1 metabolite, respectively, compared to a T_{max} of 1.5 and 1.9 h for tramadol and the M1 metabolite, respectively, with the 50 mg IR formulation (Table 49.6).[116]

Once-daily ER Ultram was formulated to counter the need for doses of IR tramadol hydrochloride (Ultram) every 6 h, improve

TABLE 49.5 Affinity Between Tramadol, Two Enantiomers, and Its Active Metabolite M1, Opioid Receptors, and Inhibition of Serotonin and Norepinephrine Reuptake

	AFFINITY FOR OPIOID RECEPTORS (Ki, mmol/L)			REUPTAKE INHIBITION	
Product	μ	δ	κ	Norepinephrine	Serotonin
(±) Tramadol	2.1	57.6	42.7	0.78	0.9
(+) Tramadol	1.3	62.4	54.0	2.51	0.53
(–) Tramadol	24.8	213	53.5	0.43	2.35
(+) M1	0.0034				
Morphine	0.00034	0.092	0.57	Inactive	Inactive
Imipramine	3.7	12.7	1.8	0.0066	0.021

K_i, Constant of inhibition.

Modified from Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43:879-923; and Mattia C, Coluzzi F. Tramadol. Focus on musculoskeletal and neuropathic pain. *Minerva Anestesiol.* 2005;71:565-584.

TABLE 49.6 Pharmacokinetic Properties of Immediate- and Extended-Release Tramadol and Its M1 Metabolite

	TRAMADOL		M1 METABOLITE	
Pharmacokinetic Parameter	Ultram ER	Ultram IR	Ultram ER	Ultram IR
C_{max} (μg/L)	335	383	95	104
C_{min} ((μg/L)	187	228	69	82
T_{max} (h)	12	1.5	15	1.9

compliance, and decrease sleep interruptions because of more stable serum concentrations. The bioavailability of ER tramadol is comparable to that of IR tramadol and demonstrates steady-state bioequivalence (area under the plasma drug concentration versus time curve and maximum concentration [C_{max}] values) compared to IR tramadol administered four times daily.[116] ER tramadol (200 mg) has a longer T_{max} (tramadol, 12 h; M1 metabolite, 15 h) than IR tramadol does (tramadol, 1.5 h; M1 metabolite, 1.9 h) but reaches steady-state plasma concentrations (tramadol and M1) within four days with once-daily dosing.

ER tramadol (100, 200, 300 mg) was found to be superior to placebo in average change from baseline pain from one through 12 weeks in a randomized trial of OA of the knee. The average ER tramadol dose was 276 mg/day.[117]

Tramadol hydrochloride ER tablets (Ryzolt, Purdue Pharma LP, Stamford, Conn, 2009) contain both IR and ER characteristics (100, 200, and 300 mg). Ryzolt is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period. The median time to peak plasma concentrations of tramadol and M1 after multiple doses of 200 mg tablets is about 4 and 5 h, respectively. Steady-state is achieved after two days with a relative bioavailability of approximately 95% with 200 mg of Ryzolt versus IR tramadol, 50 mg every 6 h (Ryzolt Package Insert, Purdue Pharma LP, 2009).

Pharmacokinetics

The maximum serum concentration of oral tramadol is reached in approximately 2 h.[118] Its mean bioavailability after a single dose is 68%,[119] and this increases to 90%–100% after multiple doses. Mean bioavailability after intramuscular administration is 100%, and after rectal administration is 78%. Tramadol is 20% bound to plasma proteins and crosses the placenta.[120] Metabolism is primarily hepatic via the CYP enzyme system. Tramadol is excreted by the kidneys (90%) and in feces (10%). Biotransformation in the liver creates 23 metabolites; the primary metabolite is *O*-desmethyltramadol (M1).[121] Polymorphism of the CYP2D6 isoenzyme in the liver (present in approximately 7%–10% of whites) may cause attenuation of analgesia in poor metabolizers. Such patients may require higher loading doses and more rescue analgesia.[122] The elimination $t_{½}$ of tramadol is 5–6 h, and that of M1 is approximately 8 h. Adjustments in dosage are required for patients with hepatic and renal failure and geriatric patients (Table 49.7).[123] Bioequivalence has been demonstrated between IR and SR-ER formulations.[107]

Management Considerations

For improved tolerability of tramadol, various titration regimens have been proposed. An alternative example of a titration schedule for the IR 50 mg tablets in patients with moderate to moderately severe chronic pain is as follows:

1. Start at 25 mg/day and titrate in 25 mg increments as separate doses every three days to reach 100 mg/day (25 mg four times daily).
2. Increase the total daily dose by 50 mg as tolerated every three days to reach 200 mg/day (50 mg four times daily).
3. After titration, tramadol, 50–100 mg, can be administered as needed for pain relief every 4–6 h, not to exceed 400 mg/day.

Patients with moderately severe pain who need more immediate pain control may benefit from a more aggressive dosing schedule. In this case, the increased risk for adverse events associated with higher initial doses must be discussed and acceptable. In this subset of patients, tramadol, 50–100 mg, may be administered as needed every 4–6 h, not to exceed 400 mg total per 24 h period.

The initial recommended dose of tramadol SR formulations is 50–100 mg twice daily. Titration to doses of 150–200 mg twice daily pending side effect tolerability and efficacy of pain relief as needed may be carried out. Tramadol ER dosage recommendations include an initial dose of 100 mg daily, with upward titration by 100 mg every five days to a maximum daily dosage of 300 mg.

Risks and Precautions

When compared to traditional opioid analgesics, tramadol retains a more favorable side effect profile and may be associated with a lower risk for addiction with chronic use.[124]

TABLE 49.7 Primary Kinetic Parameters of Tramadol in the Young, Elderly, and in Patients With Renal or Hepatic Failure*

	YOUNG HEALTHY VOLUNTEERS		OLDER HEALTHY VOLUNTEERS			
Parameter	IV (*n* = 10)	PO (*n* = 10)	PO (*n* = 12; age = 65–75 years)	PO (*n* = 8; age >75 years)	Patients With Renal Failure (IV, *n* = 12)	Patients With Hepatic Failure (PO, *n* = 10)
T_{max} (h)	—	1.9	2.0	2.1	—	1.9
C_{max} (μg/L)	409	290	324	415	894	433
AUC (μ/L × h)	3709	2488	2508	3854	7832	7848
$t_{½}β$ (h)	5.2	5.1	6.1	7.0	10.8	13.3
TC (L/h)	28.8	42.6	47.6	29.5	16.8	16.3

AUC, Area under the plasma drug concentration-versus-time curve; *TC,* total clearance; C_{max}, maximum plasma concentration; $t_{½}β$, elimination half-life; T_{max}, time necessary to reach the maximum plasma concentration.

*Depending on the patient's age and hepatic and renal failure.

From Mattia C, Coluzzi F. Tramadol. Focus on musculoskeletal and neuropathic pain. *Minerva Anestesiol.* 2005;71:565-584.

Common Side Effects

The most commonly reported side effects include nausea, vomiting, dizziness, fatigue, sweating, dry mouth, drowsiness, sedation, and orthostatic hypotension. The incidence of side effects has been reported to be as high as 16.8% in patients with chronic pain complaints. Controlled-release formulations may produce a lower incidence of side effects (6.5%).[125]

Despite its improved side effect profile and early consideration as an alternative to pure μ-opioid receptor agonist medications, reports of overdose and fatality have led to a change in the package insert information that includes a contraindication in patients with a past or present history of addiction or dependence on opioids.[113] Other more severe side effects include angioedema,[126] bleeding complications because of the increased effect of oral anticoagulants,[127] and serotonin toxicity.[128–130]

Tramadol and Serotonin Toxicity (Serotonin Syndrome)

Concomitant use of tramadol with other serotonergic medications (e.g. selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors [MAOIs], and serotonin-norepinephrine reuptake inhibitors [SNRIs]; Box 49.3) has been associated with case reports of serotonin toxicity.[131] Given that several medication classes commonly used for pain management may predispose patients to be mild to severe symptoms of serotonin toxicity, a review to gain a clearer understanding of serotonin toxicity and serotonin syndrome is in order.

Definition

Serotonin toxicity is an iatrogenic drug-induced toxidrome, a group of signs and symptoms occurring together with a particular type of chemical poisoning. Life-threatening serotonin toxicity, though rare, is usually precipitated by ingestion of MAOIs and SSRIs and leads, in some cases, to hyperpyrexia and death.[132] The pathophysiology remains unclear but may involve overstimulation of 5-HT_{1A} and 5-HT_2 receptors in the brain. Serotonin toxicity has been described by Gillman and Whyte as a triad involving neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status (Table 49.8).[130]

Sternbach proposed criteria for serotonin syndrome is one of the earlier published comprehensive reviews of serotonin syndrome.[128]

• Box 49.3 Serotonergic Drugs

- Serotonin (5-HT) Reuptake Inhibitors
  - Paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram
  - Venlafaxine, milnacipran, duloxetine
  - Clomipramine, imipramine
  - Tramadol, meperidine, fentanyl, methadone, dextromethorphan, dextropropoxyphene
- Serotonin Precursors
- 5-Hydroxytryptophan, l-Tryptophan
- 5-HT_{1A} Antagonists
- LSD, Dihydroergotamine, Bromocriptine, Buspirone
- Serotonin Releasers
  - Amphetamine, MDMA ("ecstasy")
- Monoamine Oxidase Inhibitors
  - Tranylcypromine, phenelzine, nialamide, isoniazid, iproniazid, isocarboxazid
  - Pargyline, selegiline, procarbazine
  - Moclobemide

Adapted from Gillman PK. A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action. *Biol Psychiatry.* 2006;59:1046-1051.

TABLE 49.8 Clinical Triad of Serotonin Toxicity

Parameter	Manifestations
Neuromuscular hyperactivity	Tremor, clonus, myoclonus, hyperreflexia
Autonomic hyperactivity	Diaphoresis, fever, tachycardia, tachypnea, mydriasis
Altered mental status	Agitation, excitement, confusion

In 2000 Radomski and associates[129] published an updated review of the subject with revised diagnostic criteria (Table 49.9).

Mechanisms of Serotonin Toxicity. Serotonin toxicity may be related to the mechanisms of action and potency of drugs. Tricyclic anti-depressants (TCAs) exhibit a 100-fold variability in affinity for the serotonin transporter in humans. Overdose of amitriptyline alone does not precipitate serotonin toxicity.[133] More potent TCAs, such as clomipramine, may have more potent serotonergic effects clinically and in overdose. In overdoses of SSRIs or SNRIs such as with venlafaxine alone, 15% of individuals exhibit moderate serotonin toxicity without life-threatening symptoms or pyrexia.[134] Although venlafaxine has less potency than amitriptyline at the receptor level, it precipitates serotonin toxicity more frequently than SSRIs do (30% vs. 15%). This may be related to mechanisms other than inhibition of serotonin reuptake.[135] Trazodone and nefazodone differ from TCAs and SSRIs in that they are primarily 5-HT_{2A} antagonists. Neither exhibit serotonergic side effects, nor do they induce signs of serotonin toxicity in overdose.[132]

Several other pharmacologic agents, including illicit substances, enhance 5-HT activity and must be considered in the workup for possible serotonin toxicity (e.g. buspirone, ergot alkaloids, amphetamine, cocaine, TCAs, MAOIs; Box 49.3).[136]

Clinical Use of Tramadol Formulations

Earlier reports evaluating the effectiveness of tramadol for varied painful conditions yielded conflicting results. In comparative studies of acute pain, oral tramadol was found to have efficacy similar to that of propoxyphene in a postoperative pain study and comparable efficacy as codeine for pain related to dental surgery.[137] However, tramadol hydrochloride, 50 and 100 mg, was found to have efficacy similar to that of placebo for pain after total hip arthroplasty,[138] but provided analgesia inferior to that of hydrocodone-APAP in an emergency room acute musculoskeletal pain cohort consisting of fracture, sprain-strain, and contusion.[139]

More recent clinical and evidence-based practice has found tramadol useful for a wide range of painful conditions, including OA, postamputation phantom limb and residual limb pain,[140] postoperative pain reduction after arthroscopic knee surgery,[142] and cancer-related pain.[142] Guidelines for the pharmacologic management of OA have recommended tramadol for patients who fail to achieve analgesia with APAP, COX-2 inhibitors, or NSAIDs.[143]

A 2004 Cochrane collaboration review of tramadol for neuropathic pain identified several eligible trials, including two comparing tramadol with placebo,[144,145] one comparing tramadol with clomipramine,[146] and one comparing tramadol with morphine for cancer pain.[147] Tramadol was found to be effective for the treatment of neuropathic pain based on this limited number of short-term studies (four to six weeks). The NNT for tramadol in relieving neuropathic

TABLE 49.9 Spectrum of Serotonin Syndrome

Mild State of Serotonin-Related Symptoms	Serotonin Syndrome (Full-Blown Form)		Toxic States
Single symptom may predominate	At least four major or three major and two minor of the following:		Coma
Most common are	Major	Minor	Generalized tonic-clonic seizures
Tremor Myoclonus Diaphoresis and shivering	Mental symptoms: Impaired consciousness, Elevated mood Neurologic symptoms: Myoclonus Tremor, Shivering, Rigidity, Hyperreflexia Vegetative symptoms: Fever, Sweating	Restlessness, Insomnia, Incoordination, Dilated pupils, Akathisia, Tachycardia, Tachypnea, Dyspnea, Diarrhea, Hypertension, Hypotension	Fever (may exceed 40°C) Disseminated intravascular coagulation and renal failure

Coincident with the addition of or an increase in a known serotonergic agent. Clinical features were not an integral part of the underlying psychiatric disorder before commencing the serotonergic agent. Other causes (e.g. infectious, metabolic or endocrine, substance abuse, or withdrawal) have been ruled out. A neuroleptic drug has not been started or increased in dosage before the onset of the signs and symptoms listed.

From Gnanadesigan N, Espinoza RT, Smith R, et al. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? J Am Med Dir Assoc 2005;6:265-269.

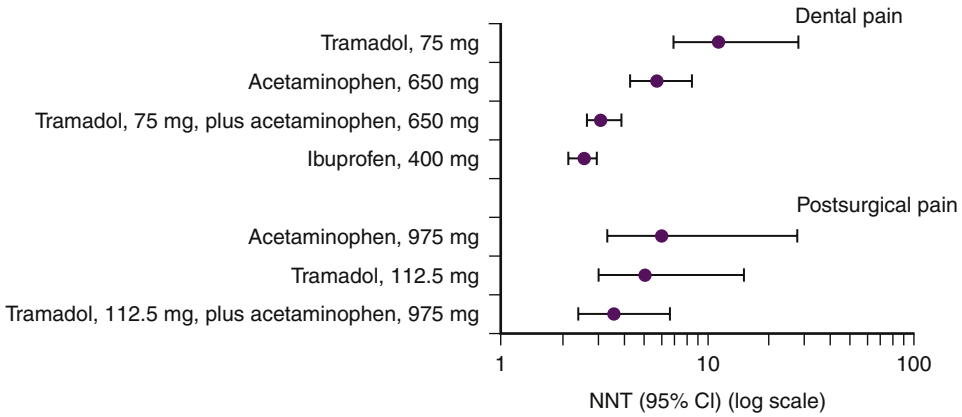
pain states (3.5) was similar to that for other commonly used medications: 2.4 for TCAs, 2.5 for carbamazepine, and 3.7 for gabapentin.

Tramadol-Acetaminophen

Several different strengths of combination tramadol and APAP compounds are available in the United States and Europe. The combination takes advantage of the potential synergy between the two compounds demonstrated in animal and human models, with an initial onset of analgesia with APAP (20 min) followed by tramadol (approximately 50 min).[148] A meta-analysis of dental pain has demonstrated that the combination of APAP plus tramadol has a similar rapid onset of efficacy as paracetamol alone, but levels of analgesia are maintained for a longer period than with tramadol alone.[149] Tramadol-APAP combination products contain less tramadol by dose (in the United States, 37.5 vs. 50 mg) and relatively less APAP (325 vs. 500 mg [extra strength APAP]) and thus may lower the potential incidence of organ toxicity (liver) when taken within the range of recommended doses.[107] Tramadol-APAP combination products have demonstrated efficacy for acute and chronic pain conditions.[150] Combination tramadol, 37.5 mg, plus APAP, 325 mg, may provide analgesia equivalent to codeine and APAP in patients with chronic OA, but with greater tolerability.[151] The most common treatment-related adverse events include somnolence, nausea, and constipation with a mean dosage of 4.1 tablets daily.[152] Figure 49.4 illustrates NNT data from a meta-analysis evaluating the efficacy of a tramadol-APAP combination for moderate to severe postoperative pain.[153]

Oral Steroids

The first glucocorticoid was isolated in 1935. This naturally occurring corticosteroid, cortisone, was later synthesized in the laboratory in 1944. Four years later, Hench and colleagues at the Mayo Clinic could obtain a portion of the synthetic cortisone available from Merck for clinical trial use. They injected the "compound E" (cortisone) into patients with rheumatoid arthritis. The patients experienced dramatic pain reduction and remarkable improvement in their functional mobility. However, when the supplies ran out just one week later, all the treated patients went into remission.[154] This report led not only to the widespread use of cortisone for the treatment of rheumatologic conditions but also earned Hench a joint award (along with Kendall and Reichstein) of the Nobel Prize in Medicine and Physiology in 1950. As oral steroid preparations evolved, their use increased in addition to injection therapy to produce systemic levels for chronic treatment regimens. Pulsed dosing schedules are now routinely used for disease



• **Figure 49.4** Meta-analysis evaluating a tramadol-acetaminophen combination for moderate to severe postoperative pain. *CI,* Confidence interval; *NNT,* number needed to treat. (From Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage.* 2002;23:121–130.)

management and episodic flares of various conditions, including rheumatic, pulmonary, dermatologic, neurologic, ophthalmologic, hematologic, and endocrine disorders. Exogenous glucocorticoid administration has been shown to have a suppressive effect on the hypothalamic-pituitary-adrenal (HPA) axis. Some believe that this can occur in as few as five days when using high supraphysiologic doses, whereas at physiologic doses, this may not occur for three to four weeks. Thus a tapered dosing schedule is typically recommended when treatment exceeds two to three weeks.[155] The use of steroids for the treatment of painful conditions is largely based on the premise that there is an inflammatory role in the mediation of pain.[156] Chronic oral steroid therapy is used for the treatment of rheumatologic inflammatory conditions (e.g. rheumatoid arthritis, polymyalgia rheumatica, Crohn's disease) and cancer pain. In addition, oral steroids are commonly used in short-term or pulsed dosing schedules for conditions such as complex regional pain syndrome (CRPS), rheumatoid arthritis flares, gouty or OA flares, painful radiculopathy, bursitis, carpal tunnel syndrome, and other acute or chronic musculoskeletal conditions.[157-159]

Mechanism of Action and Description

Adrenocortical steroids such as prednisone, methylprednisolone, and dexamethasone act by inhibiting multiple cellular mechanisms, including accumulation of inflammatory cells at sites of inflammation, macrophage phagocytosis, lysosomal enzyme release and synthesis, and release of mediators of inflammation. Regarding their ability to attenuate pain responses, this action is probably related to their strong anti-inflammatory action. Steroids suppress or prevent cell-mediated immune responses and decrease or prevent tissue response to the inflammatory process. The mechanisms for reduction of cancer pain are thought to be secondary to inhibition of PG synthesis and reduction in peritumor and perineural edema by decreasing capillary permeability.[156]

Oral prednisone is readily absorbed in the GI tract. It is highly protein-bound (up to 70%–90%) and is distributed widely in various tissues. The plasma $t_{½}$ of prednisone is 3.4–4 h, with a biologic $t_{½}$ of 18–36 h. It is metabolized in the liver to its active metabolite prednisolone, which is further metabolized to inactive compounds. The active metabolite and inactive compounds are excreted in urine, and the drug is not removed by hemodialysis.[160]

The pharmacodynamics of commonly used glucocorticoids is presented in Table 49.10.

Prednisone tablets are available in multiple dosage forms ranging from 2.5–50 mg tablets. Other glucocorticoids commonly prescribed for painful conditions include methylprednisolone (Medrol Dosepak) and dexamethasone (Table 49.11). The Medrol Dosepak consists of 21 × 4 mg tablets taken in a tapering fashion from six tablets on day one to one tablet on day six. See Box 49.4 for common glucocorticoid dosing schedules.

Risks and Precautions

In general, long-term administration at physiologic replacement doses does not lead to adverse effects. Similarly, short-term dosing at supraphysiologic levels typically does not cause adverse effects. Many have recommended a tapering dose schedule to avoid glucocorticoid withdrawal, which can occur in as few as five days at high supraphysiologic doses or in three to four weeks at physiologic doses.[155] Suppression of the HPA axis can persist for up to 12 months after cessation of prolonged corticosteroid therapy, and supplementation may be required during periods of physiologic stress such as surgery, acute blood loss, or infection. Because of the depression and prevention of cell-mediated immune responses, oral corticosteroids are not well tolerated by patients with immunocompromised states, whether acute or chronic. However, they do play an adjuvant role in the management of cancer pain.[162] In such cases, new pain complaints in cancer patients or palliative care patients must be monitored vigilantly because, in the presence of opioid analgesics and corticosteroid therapy, symptoms may be less severe and related to a new diagnosis, such as appendicitis.[162]

A population-based study examining more than 2400 patients maintained on long-term oral glucocorticoid therapy found that side effects are associated with cumulative and average doses in a dose-dependent fashion.[163] The study allowed the use of varied glucocorticoid preparations and converted them into a prednisone-equivalent dose. The most common side effects, with approximate prevalence, included weight gain (70%), skin bruising (53%), sleep disturbance (45%), mood symptoms (42%), cataracts (15%), acne (15%), and fractures (12%). An increasing daily dosage was more significantly associated with fractures and sleep disturbance than was an increased duration of use.[163]

TABLE 49.10 Pharmacodynamics of Common Glucocorticoids

Agent	Equivalent Glucocorticoid Dose (mg)	Relative Glucocorticoid Activity	Relative Mineralocorticoid Activity*	Relative Half-Life in Plasma (h)	Biologic Half-Life (h)
Cortisone	25	0.8	0.8	0.5	8–12
Cortisol	20	1	1	1.5–2	8–12
Methylprednisolone	4	5	0.5	>3.5	18–36
Prednisolone	5	4	0.6	2.1–3.5	18–36
Prednisone	5	4	0.6	3.4–3.8	18–36
Triamcinolone	4	5	0	2–5	18–36
Dexamethasone	0.75	20–30	0	3–4.5	36–54
Betamethasone	0.6	20–30	0	3–5	36–54

* Clinically—sodium and water retention, potassium depletion.

Adapted from Jacobs JWD, Bijlsma JWJ. Glucocorticoid therapy. In: W Kelly, E Harris, S Ruddy, et al. (eds). *Kelly's Textbook of Rheumatology*. 7th ed. Philadelphia: Saunders; 2005: Table 57-1.)

TABLE 49.11 Commonly Prescribed Oral Glucocorticoids

Agent	Trade Name	Available Dose Form
Methylprednisolone	Medrol	2, 4, 8, 16, 24, 32 mg tablets
Prednisone	Deltasone, Sterapred	2.5, 5, 10, 20, 50 mg tablets
	Prednisone Intensol (oral concentrate)	5 mg/mL
Dexamethasone	Decadron	0.25, 0.5, 0.75, 1.5, 4, 8 mg tablets
	Decadron elixir (oral concentrate)	0.5 mg/5 mL

• Box 49.4 Common Glucocorticoid Dosing Schedules

- Prednisone taper—prednisone, 10 mg tablets
  - Three tablets PO bid × four days, two tablets PO bid × three days, one tablet PO bid × three days
- Medrol Dosepak—methylprednisolone, 4 mg tablets
  - Day one: two tablets before breakfast, one tablet after lunch and dinner, and two tablets at bedtime (total = six tablets). If given later in the day, may take all six tablets at once or in divided doses
  - Day two: one tablet before breakfast, one tablet after lunch and dinner, and two tablets at bedtime
  - Day three: same as day two, except one tablet at bedtime
  - Day four: one tablet before breakfast, after lunch, and at bedtime
  - Day five: one tablet after breakfast and at bedtime
  - Day six: one tablet after breakfast
- Dexamethasone taper—dexamethasone, 8 mg tablets
  - Tapering schedule over seven days: 64, 32, 24, 16, 8, 8, 8 mg

Prednisone use during pregnancy is schedule D during the first trimester and schedule C in the second and third trimesters. First trimester exposure to systemic corticosteroids (category C) has been associated with intrauterine growth retardation and an increased incidence of cleft lip, with or without cleft palate. If necessary, the maternal benefits of short courses of oral corticosteroids may outweigh the fetal risks when given beyond the first trimester.[165]

Clinical Use

Oral corticosteroids have a limited role in the treatment of painful conditions. They may be useful in the treatment of acute painful inflammatory conditions, including CRPS, carpal tunnel syndrome, rotator cuff arthropathy-adhesive capsulitis, and painful cervical or lumbar radiculopathy. Steroids have been and continue to be administered by multiple routes for the treatment of CRPS.

An animal study of the effects of chronic methylprednisolone treatment on the rat CRPS type 1 model (tibia fracture) has revealed that glucocorticoids reverse hind paw edema and warmth after fracture, with persistent effects occurring after discontinuation of treatment. However, glucocorticoid treatment does not affect the allodynia, hind paw unweighting, or periarticular bone loss observed after tibia fracture.[166] Early reports reported success with systemic steroids.[167] Christensen and coworkers[160] studied 23 patients and reported that 30 mg/day of oral prednisone is significantly better than placebo based on their stated clinical outcome measures. Braus and colleagues[167] studied the effects of methylprednisolone, 32 mg/day for two weeks, followed by a taper over two weeks, for the treatment of CRPS in post-stroke patients. This randomized study showed a significant clinical improvement in the steroid-treated patients at four weeks. More recent studies showed the efficacy of oral steroids in CRPS. Jamroz et al. treated CRPS patients with a typical prednisone regimen (60 mg followed by a taper of 5 mg per day until 20 mg, 40 mg before the taper was used in elderly, adolescent, and diabetic patients).[168] Of the 39 patients, 19 (49%) reported complete pain relief, and 17 patients reported functional recovery. They noted that earlier treatment resulted in better outcomes, confirming an earlier study that showed limited efficacy of steroids in treating CRPS of more than three months.[169] It appears that a low dose oral steroid regimen (200 mg total dose: 30 mg for three days, 20 mg over three days, 10 mg for three days, 5 mg from day ten to day 14, then discontinued) is comparable to that of a high-dose regimen (450 mg total dose) in alleviating symptoms in patients with CRPS I.[170]

The use of minor analgesics in the cancer pain population is common. The most commonly used opioid co-analgesics are NSAIDs and APAP, but up to 39% of cancer patients take various types of corticosteroids, with dexamethasone being the most common formulation. Conditions being treated include breast, lung, and colorectal cancer. Studies have documented the usefulness of corticosteroids for the rational polypharmacy of cancer pain management.[161,171,172] Efficacy has been demonstrated for neuropathic pain caused by tumor compression (malignant compression of the spinal cord or brachial or lumbosacral plexus), tumor-induced bone pain, and hepatic capsule distention secondary to liver metastases.[156,173] In addition to NSAIDs and disease-modifying antirheumatic drugs, low dose oral corticosteroids may also help manage joint symptoms caused by chemotherapy-induced arthropathy.[174]

Recruitment of cancer pain patients can be difficult.[175] Despite the lack of controlled clinical trials, corticosteroids are frequently prescribed in an adjunctive role for palliation and control of the side effects of chemotherapy. Therefore these agents may play a dual role in selected patients. Many believe that corticosteroids may help in preventing chemotherapy-induced nausea and emesis and hypersensitivity reactions. In addition, they may also help ameliorate asthenic symptoms and fatigue, as well as stimulate appetite.[158,176] Any effect of oral steroids on cancer-related dyspnea is limited by the low quality of published studies.[177]

The use of oral glucocorticoids in the form of methylprednisolone or prednisone burst or taper is common practice in the acute treatment of disk herniation with radicular pain complaints. Despite a significant increase in studies evaluating the efficacy of fluoroscopically guided epidural steroid injections (see Chapter 65), there is a paucity of reports on the usefulness of oral or systemic corticosteroids in this pain population. In a prospective, double-blind, randomized controlled trial evaluating the use of oral corticosteroids for the treatment of radicular pain, a tapering dose of dexamethasone over seven days was not superior to a placebo for early or long-term relief of lumbosacral radicular pain.[178] However, dexamethasone was superior to placebo in reducing stretch-invoked pain during the straight-leg raise test. This study did allow the concurrent use of meperidine, oxycodone, and APAP for analgesia.[178] Systemic dexamethasone taper via the intramuscular route has been studied to a limited degree, with conflicting results.[179,180] The rationale for the use of oral corticosteroids is based on the observance that pro-inflammatory

mediators and neurosensitizing chemicals are released from the damaged intervertebral disk.[181,182]

There is a close relationship between injury and pain with most musculoskeletal injuries. Therefore individual treatments in a comprehensive management program may serve dual purposes—reducing inflammation to control local damage and concurrently reducing pain. Although few trials have evaluated the efficacy of oral corticosteroids for musculoskeletal injuries, clinical practice reveals that their use is widespread. A questionnaire-based study at a national sports medicine conference found that 59% of the physicians prescribe oral corticosteroids for musculoskeletal injuries, with prednisone being the most commonly used.[183] The study did not differentiate whether the medication was prescribed specifically for pain or its anti-inflammatory properties, but prescriptions were written equally for acute and chronic conditions.

Although the mainstays of treatment of carpal tunnel syndrome include neutral wrist splints, ergonomic evaluation and modification of biomechanics, oral NSAIDs, steroid injections, and surgical release of the transverse carpal ligament, there is evidence to suggest that oral corticosteroids may play a role in the short-term management of patients with mild to moderate symptoms and in those not interested in or awaiting surgical release of the transverse carpal ligament. Studies have examined varied dosing and duration-of-treatment regimens with prednisolone (ten days to three weeks, doses of up to 25 mg daily). The results suggest that regardless of dosing, the global symptom score is improved in patients treated with oral corticosteroid versus placebo.[157]

Short-term dosing of oral prednisolone at variable doses has been studied for adhesive capsulitis. Binder and associates[184] used 10 mg daily for four weeks, followed by 5 mg daily for two weeks. Night pain was significantly lower in the treatment group at eight weeks. However, by five months, this difference had resolved. Over the total eight-month period, no difference was found in pain at rest or with movement, range of motion, or the cumulative recovery curve between the oral steroid group and the control group, which received no specific therapy. Other studies have evaluated a three-week course of 30 mg prednisolone daily and reported a significant reduction in pain and disability, improved active range of motion, and better participant-rated improvement at three weeks. The improvements were still evident by six weeks, but none of the values were statistically significant. At 12 weeks, the placebo group was favored.[158] A review of the treatments for adhesive capsulitis showed steroids as a component of the multimodal management that includes intraarticular steroid injection, physical therapy, manipulation under anesthesia, and arthroscopic capsular release.[185]

The use of oral corticosteroids for the treatment of rheumatoid arthritis has been studied since 1949 when Hench and coworkers[186] showed the efficacy of the treatment in an uncontrolled trial. Although oral corticosteroids may show beneficial effects concerning the radiologic progress of the disease,[187] they are more commonly used during episodes of symptomatic flares to control pain or as bridge therapy with slower-acting agents.[188,189] A meta-analysis evaluating the effectiveness of low dose prednisolone versus placebo and NSAIDs found that low dose prednisolone (<15 mg daily) has greater effect than placebo and NSAIDs on joint tenderness and pain.[189] Presently, an oral steroid (prednisone) is an adjuvant treatment for rheumatoid arthritis, the main pharmacologic agent being a conventional disease-modifying agent (DMARD), either methotrexate or sulfasalazine and/or a biologic DMARD (e.g. adalimumab).[190]

Caffeine

Caffeine is an important adjuvant compound used in combination with OTC and prescription analgesics. Caffeine exhibits antinociceptive effects and analgesic properties when used in combination with opioid analgesics.[191] Caffeine combination products have been studied for several pain conditions, including headache,[192] low back pain,[193] and postpartum-related pain.[194] Caffeine (65–130 mg) was shown to increase the potency of other analgesics by 40%.[195] OTC headache medications typically include 65 or 32.5 mg caffeine combined with APAP, 250–500 mg, and/or ASA, 250–520 mg (Table 49.12).

Mechanism of Action and Description

Caffeine, a methylxanthine, is a nonselective adenosine receptor antagonist that blocks multiple adenosine receptors (A1, A2A, A2B, and A3) in peripheral tissues and the CNS.[196,197] Centrally, caffeine may increase dopamine and norepinephrine, as well as act as a vasoconstrictor of vessels, thereby contributing to its analgesic effect in certain headache conditions.[198] An animal study using a fixed dose of aspirin, APAP (paracetamol), and caffeine demonstrated increased secretion of norepinephrine and a reduction in dopamine in rat striatal tissue.[199]

Clinical Use

Older studies examining the relationship between dietary caffeine intake and chronic low back pain have yielded conflicting results.[200,201] One retrospective study showed higher consumption in patients with chronic low back pain[201] while a retrospective review showed no significant differences among the low, medium, and high caffeine consumer groups on pain severity, anxiety, distress, or sleeping patterns.[200] Caffeine, by itself, is not used to treat low back pain. Instead, it can be a component of combination therapy. A recent study showed small doses of a combination product (aspirin, acetaminophen, caffeine, and chlorpheniramine) to be as effective as 500 mg acetaminophen.[202]

Caffeinated medications, either alone or in combination, are widely used by patients in the treatment of headaches. A review showed that combinations of caffeine with analgesics (acetaminophen, ASA, ibuprofen) showed improved efficacy in tension-type headaches or migraines over analgesic medication alone.[203] Caffeine has also been recommended in the management of mild postdural puncture headaches.[204]

TABLE 49.12 Components of Caffeine-Containing Over-the-Counter Medications

Name	Caffeine (mg)	Acetaminophen (mg)	NSAID (mg)
Excedrin Tension Headache	65	500	N/A
Excedrin Migraine	65	250	250 ASA
Goody's Extra Strength Headache Powder	32.5	260	520 ASA

ASA, Acetylsalicylic acid; *N/A*, not applicable; *NSAID*, nonsteroidal anti-inflammatory drug.

Conclusion

Analgesics play an important role in the treatment of many acute and chronic pain conditions. Classically, many minor analgesics represent the first line of agents in the WHO analgesic ladder and range from OTC convenience medications to opioids, and adjuvants to treat musculoskeletal, arthritis, spine-related, and cancer pain conditions. The class of "minor analgesics" has broadened from the original WHO ladder to include tapentadol and buprenorphine products indicated for chronic pain. Though considered relatively safe compared to many other prescription-strength medications and stronger μ-opioid agonists, minor analgesics must be used with caution and require close patient monitoring. Side effects and adverse events related to common use and misuse of the medications include liver toxicity (APAP); GI, renal, and cardiac toxicity (NSAIDs and COX-2 inhibitors); and physiologic dependence, tolerance, and addiction (combination opioid analgesics, tramadol, tapentadol, and buprenorphine products).

Key Points

- Regular use of OTC analgesic medications is a common method used by patients to relieve various pain related conditions.
- Minor opioid analgesics include propoxyphene, hydrocodone, oxycodone, and tramadol, individually and in combination products.
- Two buprenorphine formulations, including a seven-day transdermal patch system and an oral buccal film, are additional minor opioid analgesics and are indicated for chronic pain and differ from sublingual formulations indicated for opioid use disorder. Buprenorphine has unique opioid receptor agonist-antagonist properties contributing to it is multi-mechanistic pharmacologic activity.
- Patients' responses to individual opioids and opioid combination products may vary significantly. This is probably explained by opioid receptor polymorphisms, differences in pharmacokinetics, and genetic variation related to enzymatic breakdown by hepatic metabolic systems.
- True serotonin toxicity and serotonin syndrome are rare but potentially deadly conditions seen in the field of pain management. They are characterized clinically by changes in mental status and autonomic and neuromuscular hyperactivity.
- Although conflicting clinical evidence exists, oral corticosteroids may be helpful for spine, musculoskeletal, and rheumatologic conditions. Prescribers should be aware of differences in specific types of steroid preparations and related variability in dosing.
- Combining caffeine with analgesics (acetaminophen, ASA, ibuprofen) results in improved efficacy in tension-type headaches or migraines over analgesic medication alone. Caffeine has also been recommended in the management of mild postdural puncture headaches.

Suggested Readings

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The U.S. Opioid Crisis and the Legal and Legislative Implications

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Introduction

The opioid crisis has had a dramatic impact on medical care in the United States, affecting all medical providers, especially pain physicians and their patients. From 1999 to 2011, oxycodone use increased by 500%, with the quadrupling of opioid-related overdose deaths during the same period.[1,2] Despite formal recognition of the opioid crisis in 2011 and subsequently reduced opioid prescriptions, 10.3 million Americans still misused opioids in 2018, 9.9 million of which inappropriately used prescription pain medications.[3] This was associated with over 48,000 opioid-related overdose deaths that year alone.[4] Clearly, despite the efforts of numerous stakeholders in the United States government and medicine, combating the opioid epidemic is still necessary. As one of these stakeholder groups, pain physicians must not only understand ongoing efforts to contend with the opioid epidemic but also their specific roles in these efforts. Additionally, pain physicians have unique concerns about the initiation or limitation of prescription opioids, as well as public perception and backlash. In this context, this chapter reviews the history of the opioid crisis, current efforts, and the legal background that underlies these interventions.

Historical Perspective

Opium use has been recorded since at least 3400 B.C. by the Sumerians in lower Mesopotamia, and its addictive properties were likely appreciated soon after.[5] While opium use spread throughout Asia and Europe during the following millennia, the first recorded "opium epidemic" occurred in China from the end of the 18th century to the beginning of the 20th century.[6] This was sparked by the introduction of smoking opium, rather than ingestion and dramatic increases in production and trade by the British.[6] By 1906, it is estimated that 13.4% of the Chinese population was addicted to opium.[6]

The United States dealt with its own opioid epidemic in the late 19th and early 20th centuries.[7] Morphine dependence increased after battlefield exposures during the civil war.[7] This was exacerbated by the release of heroin in 1898, which was purported to carry no "danger of acquiring the habit."[8] Increasing opioid use in the United States and other Western countries, along with the unprecedented crisis in China, ultimately led to the formation of an international drug control system and widespread reforms, including the criminalization of non-clinical opioid use in the United States in 1915.[6,7,9]

The next wave of United States opioid use began in the 1960s–70s, as approximately 20% of service members returned from the Vietnam War addicted to heroin.[10,11] This was followed by a period of "opiophobia," during which both patients and doctors limited prescription opioid use due to fears of iatrogenic opioid addiction.[11,12]

Recent History

The modern opioid crisis can be traced back to the publication of two now infamous scientific articles in the 1980s. The first was a letter to the editor published in the New England Journal of Medicine in 1980 by Porter and Jick, which stated the following:

> *Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well-documented addiction in patients who had no history of addiction. Addiction was considered to be major in only one instance. The drugs implicated were meperidine in two patients, percodan in one, and hydromorphone in one. We conclude that despite the widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.*[13]

The second was a retrospective review published in the International Association for the Study of Pain journal *Pain* in 1986 by Portenoy and Foley, which included 38 chronic pain patients managed with chronic opioid therapy. It concluded, "that opioid maintenance therapy can be a safe, salutary, and more humane alternative to the options of surgery or no treatment in patients with intractable non-malignant pain and no history of drug abuse."[14] These articles were widely presented and cited to support claims about the safety of chronic opioid therapy by physicians and the pharmaceutical industry.[15,16]

As "opiophobia" was being assuaged by the medical literature, the pharmaceutical industry was concurrently innovating to create theoretically less addictive opioids, leading to the introduction of OxyContin, an extended-release formulation of oxycodone, in 1995 by Purdue Pharma. This medication, an extensive advertising campaign, and sponsorship of more than 20,000 medical educational programs were associated with an acceleration in opioid prescribing beginning in 1996.[17,18] Purdue Pharma also provided financial support to multiple professional societies that

subsequently advocated for increased attention to the treatment of pain and opioid use for chronic non-cancer pain.[1,19,20] For example, the American Pain Society introduced the "pain is the Fifth Vital Sign" campaign in 1995.[21] Beyond providing education, this campaign impacted policy among the major hospital accrediting bodies: the Department of Veterans' Affairs in 1999 and the Joint Commission in 2001.[22,23] These efforts were associated with a dramatic acceleration in opioid prescribing in the inpatient and outpatient setting in the following years (Fig. 50.1).[24]

Well-meaning physicians, pharmacists, and patients who previously minimized opioids due to fears of dependence and addiction were now utilizing opioids more liberally to avoid undertreatment of pain and be concordant with contemporary guidelines. Not all parties were found to be well-meaning. However, exacerbating the growth in opioid prescriptions during this period without resulting in patient benefit. For example, Purdue Pharma paid an $8.3 billion settlement in 2020 as part of a plea deal on three felony counts of criminal wrongdoing.[25] They are not the only pharmaceutical companies to face penalties, as settlements have been reached involving Johnson & Johnson, Mallinckrodt, and Teva Pharmaceuticals.[26]

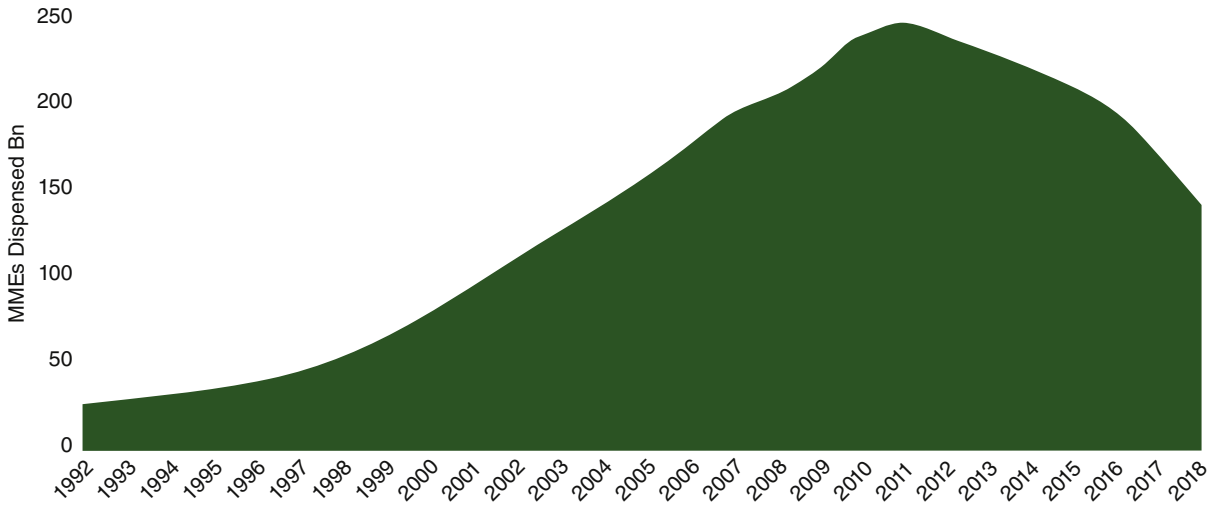
Physicians, pharmacists, physician assistants, nurses, organized crime, and street-level drug dealers have also been implicated in the spread of prescription opioids during this time.[27] For example, one "pill mill" scheme in Arkansas involved recruiters who found patients to be inappropriately prescribed large amounts of opioids by a clinic. These patients would fill these prescriptions at the pharmacy involved in the scheme. The patients would then deliver the pills to drug dealers, and all parties involved received portions of the profits.[27] Irregular, high-volume controlled substance prescription fills could theoretically be detected and reported by drug distribution companies, but this mechanism proved to be inadequate, leading to legal settlements involving the three largest drug distribution companies: AmerisourceBergen Corp., Cardinal Health Inc., and McKesson Corp.[26]

The influx of prescription opioids in the market led to a large increase in opioid exposure in the United States. Between 1988 and 1994, the prescription opioid use rate in the past 30 days among medical and non-medical users aged 20 and over was 3.4%.[28] Between 1999 and 2002, this number grew to 5.0%, and from 2003 to 2006, this rate peaked at 6.9% and persisted until at least 2012,[29] with increased opioid usage increased opioid overdose deaths among medical and non-medical users during the first wave of the opioid crisis from 1999 to 2010 (Fig. 50.2).[30]

The second wave of the opioid crisis began in 2010, with a dramatic inflection in opioid overdose deaths involving heroin.[30] The rise in heroin use and deaths has been attributed to several factors: increased availability of high-purity heroin, prescription drug abusers turning to heroin, and heroin use beginning at a younger age.[31] As a measure of availability, heroin seizures at the Southwest border increased 352% from 2008 to 2015, according to the United States Drug Enforcement Agency.[31] Additionally, as law enforcement focused on limiting the distribution of illicit prescription opioids, an unintended consequence was opioid users being shunted to cheaper and readily available heroin. Prescription pain pill abusers were 19 times more likely to start using heroin than the general public.[32] Furthermore, the average age of heroin users dropped to as low as 21.4 years old, which was associated with higher rates of polysubstance abuse and alcohol binge drinking.[32]

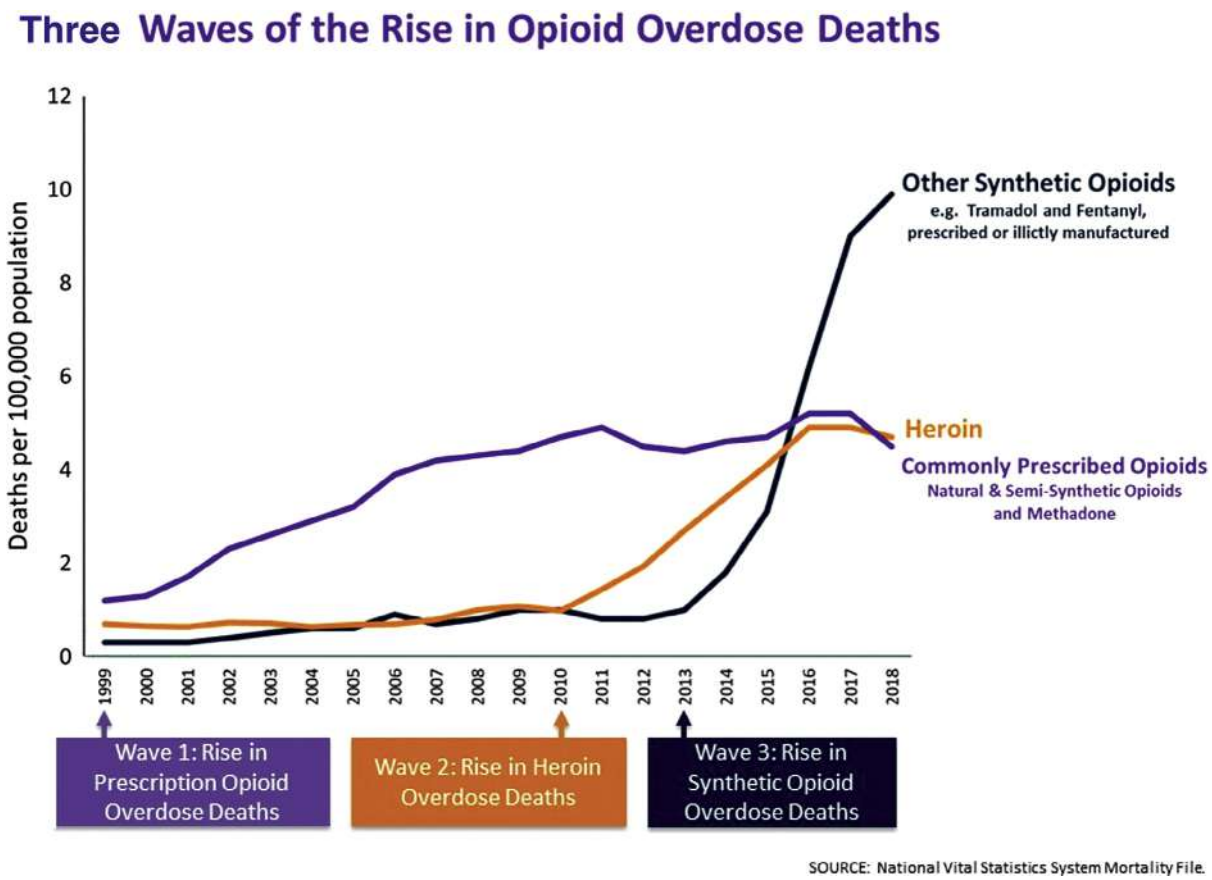
In 2011, the Obama administration formally addressed the prescription opioid epidemic and revealed a plan to combat the crisis.[33] This plan detailed broad reforms involving many governmental agencies. Most notably, it initiated diverse education efforts, invested in prescription drug monitoring programs (PDMPs), encouraged appropriate drug disposal, and removed law enforcement barriers.[33] Around this time, prescribed opioid overdose deaths stabilized, and morphine equivalents dispensed began to decline.[24,30] However, heroin use continued to grow.

In the setting of stable prescription opioid overdose deaths but increasing heroin associated deaths, the third wave of the opioid crisis began in 2013 with a rise in the use of fentanyl and other synthetic opioids.[30] Increased law enforcement efforts made the production and shipment of heroin more difficult, which may have shifted drug production toward fentanyl. Fentanyl does not require harvesting poppies, and small shipments are profitable. Furthermore, fentanyl is found to be mixed with non-opioids such as cocaine and methamphetamine, suggesting that dealers



Source: IQVIA National Prescription Audit, Dec 2017; IQVIA Xponent, Feb 2019

• **Figure 50.1** Narcotic Analgesic Dispensed Volumes in Morphine Milligram Equivalents (MME) billions. The analysis is based on opioid medicines for pain management and excludes those medicines used for medication-assisted opioid use dependency treatment or overdose recovery.



• **Figure 50.2** Opioid overdose death rates by year stratified by opioid type. (From the Centers for Disease Control and Prevention.)

may add fentanyl to non-opioids attempting to leverage its addictiveness.[34,35]

As the opioid crisis persisted, several professional organizations, states, and federal agencies began releasing opioid prescribing guidelines, but these guidelines varied in their use of evidence, methods of addressing conflicts of interest, and ultimately their specific recommendations.[36] This motivated the creation of the Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain released in 2016, which intended to advise primary care clinicians on how to avoid problematic prescribing habits for adults with chronic, non-cancer pain.[36] Although all pain medicine clinicians should be familiar with the full text of the CDC guidelines, the 12 primary recommendations are listed in Box 50.1.[36]

This guideline with explicit morphine milligram equivalent thresholds has had a dramatic impact on opioid prescriptions.[37] High-dose opioid prescriptions, concurrent opioid, and benzodiazepine prescriptions, and overall opioid prescription rates all declined more rapidly after the publication of the guideline.[37]

Before the end of his second term, President Obama signed two additional pieces of legislation into law to further combat the opioid crisis, the Comprehensive Addiction and Recovery Act (CARA) of 2016, followed by the 21st Century Cures Act.[38,39] CARA dedicated new funding toward the opioid epidemic and focused on prevention, overdose reversal, treatment, recovery, law enforcement, and criminal justice reform.[39] The 21st Century Cures Act supplemented this work with grant funding for substance abuse and mental health treatment.[38]

Current State

In January 2017, Donald Trump was inaugurated as president of the United States. By October 2017, President Trump declared the opioid crisis a public health emergency, which remained designated as an emergency until October 2018.[40] The emergency status led to reduced paperwork and wait times for several governmental efforts to address the crisis. However, the overall impact of this emergency declaration is a matter of debate.[41]

In November 2017, the President's Commission on Combating Drug Addiction and the Opioid Crisis released its final report with 56 recommendations.[42] This was followed in March 2018 by the release of President Donald J. Trump's initiative to stop opioid abuse and reduce drug supply and demand.[43] These two reports outline a variety of priorities and continue to impact actions by the administration. For example, they advocate increased funding of opioid-related government activities, a mass media prevention campaign, increasing access to treatment for substance use disorder, drug court rather than prison, legislation to assist former felons in finding work, and expanding law enforcement resources.[42,43] A progress update published in May 2019 by the Trump administration touted examples of its progress toward the goals of these reports: $6 billion in funding over two years to fight the opioid crisis, a large ad campaign, a reduction in opioids dispensed, increased arrests and seizures by law enforcement, increased use of medication-assisted treatment (MAT), increased naloxone prescription, and several other reported measures of success.[44]

• BOX 50.1 Recommendations From the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain - United States, 2016

1. Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if the benefits do not outweigh the risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long term opioid use often begins with the treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate the benefits and harms of continued therapy with patients every three months or more frequently. If benefits do not outweigh the harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or taper and discontinue opioids.
8. Before starting and periodically during the continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase the risk for opioid overdose, such as a history of overdose, history of a substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications and other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone combined with behavioral therapies) for patients with opioid use disorder.

Another effort by the Trump administration to combat the opioid crisis, the Prescription Interdiction and Litigation Task Force, was announced in February 2018. This task force aims to support local jurisdictions with the filing of lawsuits against prescription drug producers and distributors.[45] For example, the task force filed a statement of interest in a federal court case that combined over 600 lawsuits lodged by disparate government entities against opioid manufacturers.[46]

In addition to efforts to reduce opioid use, another development in the opioid crisis is a "swing of the opioid pendulum" back toward rational but slightly more liberal opioid prescribing.[47–49] Though the CDC guideline was in many respects a success, it also led to the creation of some inflexible policies and practices that were inconsistent with the original guidelines.[47–49] For example, misapplication of the guidelines affected the care of patients with cancer, sickle cell crises, and opioid use disorders.[47,50] The guidelines were also used to justify rapid tapers or complete discontinuation of opioids in some patients.[47,49] Such practices are not only difficult for patients but can also be associated with an increased risk of overdose death in high risk populations.[51] These concerns prompted several of the authors of the CDC guideline to provide further guidance regarding the proper application of the guidelines in April 2019.[47,48] Individualized approaches were emphasized, and hard limits, abrupt tapering, and sudden discontinuation of opioids were discouraged.[47,48]

At the time of writing, there is room for optimism in the current state of the opioid crisis. Prescription opioid dispensing has been declining every year since its peak in 2011, and it declined by 17% in 2018 alone.[24] Deaths from opioid-related overdoses may have also plateaued since the peak of 48,580 deaths in November 2017, although deaths from synthetic opioids continue to rise.[52] Overall life expectancy rose in 2018 for the first time since 2014. The CDC attributed this partially to decreased unintentional injuries, which includes opioid-related overdose deaths.[53] Part of the decline in opioid-related overdose deaths may be due to increased use of MAT for opioid use disorder. From 2014 to 2018, MAT prescriptions increased 47%, from 11 to 16.2 million.[24] Opioid misuse among youth in the United States is also trending down. For example, 2.7% of 12th-graders reported illicit prescription opioid use, the lowest percentage ever recorded since surveying began in 1991.[54] Despite these encouraging trends, the opioid crisis remains a significant problem. More people die from opioid-related overdoses than car accidents in the United States, and the number of opioid-related overdose deaths has remained essentially unchanged from November 2017 to August 2019.[52,55]

Legal Landscape

All past and present efforts to combat the opioid crisis are founded on a host of international treaties, federal and state laws, and legal precedent set by case law. While a full account of these influences is beyond the scope of this chapter, some of the most impactful are described in the following sections to provide context and a working understanding for the practicing pain clinician.

International

The most important international treaty affecting prescription opioid distribution is the Single Convention on Narcotic Drugs of 1961, which was signed by 186 countries.[56–58] The Single Convention encourages a balance between the dual obligations of minimizing opioid abuse and ensuring opioids are available for legitimate medical and scientific purposes.[57,58] These requirements stipulate the authorization and licensing of all parties involved in the medical distribution of opioids, a valid prescription for patients to receive opioids, and barriers to abuse that are not so high as to limit reasonable use.[57,58] Interestingly, much of the global work of the International Narcotics Control Board, the United Nations agency responsible for monitoring compliance with the Single Convention, has been focused on increasing access to opioids for appropriate medical needs.[59] While the United States battles the opioid crisis, approximately 75% of the world population is without adequate access to medications containing opioids.[59]

Federal

Until the early 20th century, opioid use was effectively unregulated in the United States.[60] Opium, morphine, or heroin could be widely obtained.[60] This changed with the passage of the Harrison Narcotics Tax Act of 1914.[9,60] Initially intended as a law to regulate the opioid market, it became interpreted by law enforcement as a prohibition of all opioid use except for the medical treatment of pain.[60] Non-prescription opioid use was outlawed within weeks, and MAT of opioid addiction was discontinued by 1924 due to interpretation of the Harrison Act.[60]

The next major piece of legislation to impact prescription opioid use in the United States was the Federal Food, Drug, and Cosmetic Act of 1962, which provided new authorities and teeth to the Food and Drug Administration (FDA).[61] Prior to this, the FDA had no authority to enforce proper manufacturing processes or regulate all marketing, for example.[62] This was eventually followed by the Food and Drug Administration Amendments Act of 2007, which was particularly relevant to opioid prescribing.[63] It gave the FDA the authority to determine if drug manufacturers must submit risk evaluation and mitigation strategies (REMS) for medications with anticipated harms.[63] Since then REMS programs have been established for a variety of opioid formulations, including transmucosal immediate-release fentanyl (TIRF) products and long-acting (LA) and extended-release (ER) products.[64,65] REMS programs involve educating patients and providers, and they may increase knowledge and reduce harm.[66] However, they also create a barrier to prescribing for some clinicians, thus limiting access for some patients.[67]

Between 1914 and 1970, 55 federal laws were passed to strengthen the Harrison Narcotics Tax Act.[60] In the context of the Single Convention, modernization of the FDA, the rise of methadone maintenance in the mid-to-late 1960s under legal ambiguity, increasing recreational drug use in the late 1960s, and the subsequent "War on Drugs," preexisting federal laws were consolidated into the Comprehensive Drug Abuse Prevention and Control Act of 1970, which included the Controlled Substances Act (CSA).[60,68–70]

The CSA is now the primary law dictating prescription opioid distribution in the United States, and it is primarily enforced by the Drug Enforcement Administration (DEA).[68,71] Importantly, while trying to prevent the illicit distribution of opioids and other controlled substances, the CSA aims to conform to the Single Convention and ensure the availability of opioids for legitimate medical purposes.[68,72] Furthermore, while controlling the distribution of prescription opioids, the CSA does not define or give the DEA the authority to define appropriate medical practices. This responsibility is left to the state.[68,71]

The CSA is responsible for establishing the one through five scheduling classification schema of controlled substances.[68] Controlled substances are placed into one of the schedules based on medical usefulness and abuse potential (Box 50.2).[68] Briefly, Schedule I drugs are those with no accepted medical use and a high abuse potential.[68] However, there is debate about which substances should belong in this class.[73] For example, it includes "marijuana," which has established medical value for a variety of conditions.[68,73] Schedule II drugs are those with medical use and high abuse potential, which includes most opioids.[68] Notably, Schedule II drugs can only be prescribed for up to 30 days and cannot be refilled, though they can be prescribed sequentially for up to 90 days.[68,74] Schedule III medications have less abuse potential and include codeine combination products as well as buprenorphine.[71] Schedule IV medications have even lower abuse potential and include tramadol.[71] Both Schedule III and IV prescriptions can be refilled up to five times.[68] Lastly, Schedule V includes the least abusable substances, like compounds with very low doses of opioids used for cough suppression or as antidiarrheals.[71]

Another significant component of the CSA was the explicit legalization of opioid prescription for addiction treatment, not just for pain.[68] Opioid maintenance for addiction was distinguished from prescribing for pain. However, all sites must register as opioid treatment programs to be allowed to prescribe opioid detoxification or maintenance.[68]

State

The power to regulate medical practice lies with states and their medical licensing boards, either through legislation or regulations. These regulatory powers must comply with federal law and the Single Convention.[71] Though each states' laws differ, nearly every state has adopted some form of the Federation of State Medical Boards' 2017 Guidelines for the Chronic Use of Opioid Analgesics.[71,76] These guidelines are intended as a resource for state medical boards in assessing physician use of opioids in a "medically appropriate manner."[76] Every clinician who manages pain should be aware of the laws and regulations specific to his or her state. Nevertheless, a variety of legal issues apply to all states.[77]

Maintaining a balance between the availability and regulation of opioids remains important, especially in the age of the opioid epidemic.[77] For example, primary care providers in Washington must consult a pain physician for patients who receive a morphine equivalent dose (MED) greater than 120 mg.[78] However, if pain physician consultations are not accessible due to distance or insurance coverage, this requirement could create an imbalance. Imbalance can also be created by overly restrictive prescription limitations in terms of quantities or days.[77]

Another issue is state classifications of addiction.[77] Defining addiction by physiologic dependence or tolerance, without the necessary behavioral components, can falsely label patients on chronic opioid therapy as "addicts."[77,79] Beyond being incorrect, this can have other legal ramifications depending on opioid prescribing laws targeted toward those with true substance abuse disorders.[71,77] Furthermore, for those with substance abuse disorders, laws should aim to limit abuse, but they should not prevent patients with substance abuse disorders from receiving adequate treatment for pain.[71,77]

Of equal importance to how laws and regulations are written is how they are interpreted. Regardless of what is intended,

• BOX 50.2 The United States Drug Enforcement Administration Drug Scheduling[75]

Schedule I

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Examples of Schedule I drugs are as follows:

Heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote.

Schedule II

Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, potentially leading to severe psychological or physical dependence. These drugs are considered dangerous. Some examples of Schedule II drugs are as follows:

Combination products with less than 15 mg of hydrocodone per dosage unit (Vicodin), cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin.

Schedule III

Schedule III drugs, substances, or chemicals are defined as drugs with moderate to low potential for physical and psychological dependence. Schedule III drug abuse potential is less than that of Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are as follows:

Products containing less than 90 mg of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone.

Schedule IV

Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and a low risk of dependence. Some examples of Schedule IV drugs are as follows:

Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol.

Schedule V

Schedule V drugs, substances, or chemicals are defined as drugs with a lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are as follows:

Cough preparations with less than 200 mg of codeine or per 100 mL (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin.

practitioner misperceptions of policy can lead to reluctance to prescribe opioids, potentially limiting access.[71] In this sense, legal ambiguity itself is an issue within state control.

Beyond laws and regulations, states also play a critical role in maintaining PDMPs. Forty-nine states, the District of Columbia, and Guam have operational PDMPs.[80] The lone missing state is Missouri, though it has several city-level and county-level PDMPs.[81] Ideally, all PDMPs would provide near-real-time information, be readily accessible by clinicians at the time of prescription writing, and extract information from neighboring jurisdictions, if not all jurisdictions.[76]

Legal Decisions

In addition to adopted legislation, there is a host of litigation that has set precedents relevant to opioid prescriptions. While many could be discussed, three illustrative cases are presented. The binding nature of case law depends on the jurisdiction of pending litigation, but these cases demonstrate the range of perspectives adopted by the courts.

The first is *the Estate of Henry James v. Hillhaven Corporation*, which was decided in North Carolina in 1991. In this case, a patient with metastatic cancer achieved pain control in the hospital with opioid therapy. However, when he was admitted to a skilled nursing facility, a nurse determined that he was addicted to morphine and completely replaced his opioid with a sedative. After his stay, his estate sued the facility, arguing that a standard of care existed, was not met, and led to suffering. His estate won this case at $15 million. This case suggests that patients have the right to effective pain relief.[82]

United States v. Rosen is a case decided by the United States Court of Appeal for the Fifth Circuit in 1978 on the opposite end of the prescribing spectrum. Dr. Rosen heavily prescribed medications as part of a weight loss practice, and he was charged with 25 counts of distribution of controlled substances, leading to a five-year prison sentence.[83] To be convicted of these charges, the prosecution had to prove that he prescribed these medications without a legitimate medical purpose. By showing that his behavior was far outside standard medical practice, he was not treated as just a negligent physician who would be liable to malpractice or revocation of his license. Instead, he was prosecuted as a drug dealer and subject to criminal penalties. This case suggests that prescribing physicians can be treated as criminals if their behavior is far from the standard of care.[71]

An additional notable case was the DEA administrative decision to grant a DEA certificate of registration to Dr. David Gillis in 1993. The DEA initially attempted to deny Dr. Gillis the opportunity to register for a DEA license because they claimed he was prescribing opioids to known drug abusers. However, because it was shown that the physician was prescribing to treat pain, the physician's actions were deemed legitimate by an administrative decision.[84] This clarified the ability to prescribe to treat pain regardless of addiction. Ultimately, the purpose of prescribing is most relevant, not the patient himself/herself.[71]

Conclusions

Opioids play a complex role in human history. They are undoubtedly essential tools in a physician's toolbox, especially when treating acute pain. However, their addictive nature and lethality have plagued humanity. To remedy the current opioid crisis, a broad swath of stakeholders is actively working under an evolving legal and regulatory landscape. As clinicians, we must understand and assist these efforts for the betterment of our patients, as well as the community at large.

Key Points

- Opioids are an essential tool in a physician's toolbox, but their addictive nature and lethality have also plagued humanity throughout history.
- The development of OxyContin in 1996, combined with an advertising campaign and sponsorship of more than 20,000 educational programs, led to an acceleration in opioid prescription.
- The first wave of the opioid epidemic began in 1999, with a large increase in prescription opioid overdose deaths. The second wave of the opioid epidemic began in 2010, as former prescription opioid users transitioned to heroin. The third wave of the opioid epidemic started in 2013, as fentanyl became more abundant in the illicit opioid supply.
- The CDC guidelines for opioid prescription were released in 2016 and led to a decline in opioid use. However, clarification was released in 2019, emphasizing individualized approaches and the avoidance of hard limits, abrupt tapering, and sudden discontinuation of opioids.
- 10.3 million Americans misused opioids in 2018, 9.9 million of which misused prescription pain medications. This was associated with over 48,000 opioid-related overdose deaths that year alone.
- Ultimately, pharmaceutical companies, drug distributors, pharmacies, physicians, nurses, and pharmacists share some responsibility for the opioid epidemic.
- Current and future efforts to combat the opioid crisis are necessary, but all efforts must maintain a balance between preventing the abuse of opioids and making them available for legitimate medical purposes.
- Pain physicians must understand the ongoing efforts to contend with the opioid epidemic and their roles in these efforts.

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Evaluation for Opioid Management: Opioid Misuse Assessment Tools and Drug Testing in Pain Management

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Background and Overview of Pain Issues

Chronic pain, defined typically as pain lasting longer than three months,[1] is a global problem that can negatively impact every facet of daily living.[2,3] It is estimated that in the United States, there are between 50 and 100 million adults with chronic pain, affecting more individuals than heart disease, diabetes, and cancer combined.[4] Chronic pain contributes to psychological distress, social isolation, sleep disturbances, and job loss and is the major reason people visit their primary care physicians.[5] Chronic pain is known to interfere with routine daily activities and negatively affect appetite, mood, energy level, and sexual activity. Persons with chronic pain often have recurrent worried thoughts about finances, family interactions, and future disability.[6] It is estimated that chronic pain costs up to $635 billion annually in healthcare expenses and lost productivity in the United States alone-more than any other chronic disease.[4] Treatment for chronic pain is three times more expensive than treatment for similar conditions without chronic pain.[7] The burden caused by chronic pain is escalating because of the increasing average age and associated medical comorbidities that come with living longer.[5] Chronic pain represents a significant public health challenge because of the lack of adequate assessment and treatment and noted disparities in the experience of pain among population subgroups.[4]

Opioids are known to be useful in the treatment of acute and cancer-related pain.[8] It is estimated that between 5 and 8 million Americans use opioids for the management of chronic non-cancer pain.[9] More recently, providers have become reluctant to prescribe opioids for the treatment of chronic non-cancer pain because of concerns regarding tolerance, dependence, and addiction, as well as uncertainty about their long term benefit in this setting.[10] There has been a dramatic increase in opioid-related deaths,[11] and significant media attention to concerns of addiction predominately from prescription opioid use,[12] resulting in what has been known as the "opioid crisis."[13,14] This crisis was attributed, in part, to the steady increase in the use of prescription opioids in the United States,[15,16] that was seen as the main contributing factor to the increased incidence of prescription opioid abuse,[17] and opioid-related overdoses and hospitalizations.[11,18] In the United States, prescription opioids are responsible for more deaths than cocaine and heroin combined and are known as the most abused drug class.[19,20] Although this percentage has been gradually decreasing, for a time the United States consumed an estimated 80% of all prescription opioids worldwide.[21] Persons who abused prescription opioids in the past believed that they were safer and more accessible than street drugs, often available as left-over medication from family and friends, and perceived to be pure because of increased regulations on the manufacturing of prescription drugs. Many providers who manage patients with chronic pain have limited training in the assessment and treatment of pain. They are unaware of risk assessment strategies and methods for close monitoring of persons receiving prescription opioids. Studies have shown that those at risk of misusing opioids tend to be the ones most likely to be prescribed opioids for pain.[22]

In this chapter, we present definitions of terms related to opioid misuse and abuse and share information on the prevalence of prescription opioid misuse. We will give an overview of risk factors and risk assessment strategies designed to improve opioid compliance. Last, we will briefly discuss behavioral interventions designed to improve and maximize compliance and explore future considerations for improving patient engagement.

Terminology

It is important to have a clear understanding of the terms used to describe the problem of prescription opioid abuse. Often abuse is used to describe non-medical use, misuse, and/or addiction. Therefore it is important to first define the terms used to describe this multidimensional problem. The definitions used in this chapter are presented in Table 51.1. For the purpose of this chapter, we define abuse as any repeated use of an illegal drug or the intentional self-administration of a medication for the express purpose of altering one's state of consciousness and achieving euphoria (such as getting high).[23,24] In contrast, misuse is the use of any drug in a manner other than indicated or prescribed, but not necessarily with unlawful intent. For example, a patient may split a pill to reduce the dose or double-up on the dose for added pain relief. In contrast, addiction is a primary,

TABLE 51.1 Definitions of Terms

Term	Definition
Aberrant drug-related behavior	Any behaviors that suggest the *potential* presence of substance abuse or addiction.
Abuse	Use of an illegal drug or the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness, e.g. getting high.
Addiction	A primary, chronic, neurobiologic syndrome characterized by behaviors that include one or more of the following: (1) impaired control over drug use, (2) compulsive use (that may interfere with function and performance of regular duties), (3) continued use despite harm, and (4) craving (e.g. preoccupation and obsession).
Diversion	The transfer of a controlled substance from a lawful to an unlawful channel of distribution or use.
Misuse	Use of any drug in a manner other than indicated or prescribed, but not necessarily with unlawful intent.
Physical dependence	A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of drug, and/or administration of an antagonist.
Pseudoaddiction	The presence of aberrant behaviors suggestive of abuse (e.g. "doctor shopping") that in reality signifies undertreated pain.
Tolerance	The need for increasing doses to obtain the same effect.

chronic, neurobiologic syndrome characterized by behaviors that include impaired control over drug use, compulsive use (that may interfere with function and performance of regular duties), craving, and continued use despite harm. Addiction refers to a behavioral pattern of substance abuse characterized by overwhelming involvement with the use of a drug. The compulsive use of the drug results in physical, psychological, and social harm to the user, and use continues despite this harm. Iatrogenic addiction is an addiction that results from exposure to opioids for acute pain.

Aberrant drug-related behaviors are any behaviors that suggest the potential presence of substance abuse or addiction (e.g. "doctor shopping").[10,25–27] Pseudoaddiction has been a term used to describe behavior that was thought to reflect addiction but which disappeared after suitable amounts of medication was given for the treatment of pain.[28] For example, it was thought that any patient with undertreated pain, due perhaps to the provider's fear of addiction or abuse, who sought care from another physician for the purpose of adequately relieving pain might have had signs of pseudoaddiction. It is uncertain whether this condition exists and was used in the past to support the increased use of opioids. However, this term has recently gone out of fashion.

Physical dependence is a condition of physiologic withdrawal after the dose of many medications, including an opioid, is rapidly reduced. Withdrawal symptoms are generally specific for the class of substance involved, e.g. opioids, and benzodiazepines. This is noted to occur among all mammals who have been administered opioids over time. After a rapid dose reduction, including decreased blood levels of an opioid and/or administration of an antagonist, signs of withdrawal may include diarrhea, rhinorrhea, piloerection, insomnia, irritability, and psychomotor agitation.[29,30] The effects of opioid withdrawal can be reduced by gradually tapering the dose downward over an extended period. Physical dependence is a common condition of anyone actively using opioid therapy on a chronic basis and is not considered an addiction. Tolerance is another phenomenon associated with the long term use of opioids, where there is a need for increasing doses to obtain the same effect.[23,24,31]

Diversion has been defined by the Drug Enforcement Administration as a redirection of a controlled substance for use in an unlawful manner.[32] Drugs can be diverted by being stolen or being sold on the street. Additionally, it includes obtaining the medication from a legitimate source for legitimate means but used for an illegal purpose such as selling the drug to get high. Among adults 50 years and older, the main source of receiving opioids is through a physician's prescription, with this age group making up 25% of the individuals who self-reported opioid misuse. For individuals under 50 years old, it is more commonly reported that opioids were obtained from an illegal source.[33]

Prevalence of Prescription Opioid Misuse and Addiction

Addiction is generally understood to be a chronic condition from which recovery is possible. However, the underlying neurobiologic dysfunction, once manifested, is believed to persist.[12,34] Therefore the prescription of opioid analgesics to a patient with a predisposition for or history of addiction could initiate an addictive disorder or relapse. Some of the disparity between the results of studies reporting an extremely low risk of addiction for hospitalized patients and the high proportion of substance abuse in the general population can be explained by the unreliable methodology of existing surveys of iatrogenic addiction (e.g. addiction as a result of exposure to opioids for acute pain) in hospitalized patients.

Although there has been a lack of high-quality evidence or consistent findings on the prevalence of substance abuse among persons with chronic pain, there is a trend to suggest that escalating doses of opioids among those with chronic non-cancer pain is associated with increased risks of substance use disorder and opioid-related adverse outcomes.[19] Rates of opioid misuse and addiction among persons with chronic pain have been varied and were thought to be much higher than initially published in the 1980s.[15,21,35] One reason given for the variable rates of addiction was because they were not obtained from representative chronic pain patients,[30] and vague definitions of addiction were used.[36] The studies in question examined the retrospective prevalence of cases rather than the incidence and onset of new cases of addiction.[37,38] Additionally, those

perceived to have mental health issues or substance abuse problems were often excluded. Patients with chronic pain often present with a mood disorder and a comorbid psychiatric condition, and they are likely to be prescribed opioids. Thus it has been assumed that early rates of prescription opioid abuse were low. Unfortunately, there are limited large-scale studies designed to determine reliable rates of addiction among individuals treated for chronic pain. A systematic review and meta-analysis of the incidence of iatrogenic opioid dependence and abuse revealed a pooled incidence of 4.7%.[36] The authors found that when diagnostic and statistical manual of mental disorders (DSM) criteria were used, the rates of addiction were higher (11.3%) than when using ICD-9 criteria (1.3%). Vowles et al.[39] found wide variability in prescription opioid addiction rates across studies (i.e. range: 8%–34.1%). The differences observed in opioid addiction rates are assumed to be due, in part, to differences in study populations, study designs, and settings in which opioids were prescribed. Unfortunately, when addiction is based on DSM-V criteria (opioid use disorder), the reported addiction rates tend to be much higher.

Prescription Opioid Misuse Risk Factors

Guidelines from the Centers for Disease Control (CDC) recommend that healthcare providers make every effort to identify abuse and possible diversion of prescription opioids.[18,32] The guidelines suggest that particular problematic behavior, such as seeking prescriptions from multiple providers, using illicit drugs, selling or diverting medications, snorting or injecting medications, and using drugs in a manner other than the way they were intended, should be carefully monitored. Despite the need to identify misuse of opioids and limit inappropriate prescribing, healthcare professionals need to provide appropriate pain relief for individuals who have evidence of genuine pain problems.[29]

Additional problems associated with chronic use of opioids include psychological dependence,[40,41] impaired cognition, problems with psychomotor function,[42] and possible development of opioid-induced hyperalgesia (OIH).[43,44] High-dose opioids, which some define as greater than 180 mg morphine equivalent a day, have been known to lead to sleep apnea, respiratory depression, and disordered breathing. Of most concern is the risk that greater dependence on opioids can lead to addiction.[12,21] This strongly supports the need for risk assessment at the point of opioid initiation and for continued careful monitoring,[15,45,46] maintaining lower doses of opioids when indicated,[18,20,47] tracking compliance,[10,24,48] and offering an interdisciplinary approach to pain management.[49,50]

There are identifiable characteristics of those individuals who are at lower risk of misusing opioids. In particular, those who are older, who present with stable mood, have a record of being reliable in keeping appointments and in following medical recommendations, who have no history of overusing medications, who have no cognitive deficits, and who are generally pleasant are at lower risk of opioid misuse.[20,50] Equally, there are characteristics of those who are at higher risk of medication misuse. These include those who are younger and have a history of risk-taking behavior, who have a history of legal problems, who are in frequent contact with others who misuse substances, who have a mood disorder, and who have a personal or family history of substance abuse.[50] Additional factors include previous drug or alcohol rehabilitation, history of early childhood abuse and trauma, multiple stressors, smoking cigarettes, or regularly using other substances that lead to dependence (Table 51.2).[51–53]

TABLE 51.2 Risk Factors for Opioid Misuse

- Family history of substance abuse
- Personal history of substance abuse
- Young age
- Mood disorder such as extreme anxiety, depression, and/or irritability
- History of criminal activity and/or legal problems, including driving under the influence
- History of childhood abuse and/or trauma
- Regular contact with others who misuse substances
- Problems with past employers, family members, and friends (personality disorder)
- Risk-taking or thrill-seeking behavior
- Heavy tobacco use or use of substances that lead to dependence
- Psychosocial stressors
- Prior drug and/or alcohol rehabilitation

An important reminder to anyone prescribed opioids for chronic pain is that they ultimately are the ones who must manage the opioids in a responsible manner, and they need to be vigilant about factors that may contribute to opioid abuse. It is important to remind anyone using prescription opioids for pain of factors that may increase their susceptibility of encountering problems. These factors may include impulsivity,[54,55] predispositions to self-medicate symptoms of anxiety or depression,[56,57] and experiencing drug liking or craving of the medications.[58,59]

Negative Affect and Opioid Misuse

We know that there is an overlap between chronic pain and mood disorders, including depression, anxiety, and irritability perceived by some to be a normal response to prolonged pain.[60,61] Psychiatric comorbidity is common among chronic pain patients.[62] It is estimated that 30% to 40% of pain patients in primary care centers have a significant psychiatric comorbidity and show signs of negative affect.[63,64] These percentages increase between 50% and 75% among patients treated at specialty pain centers.[65] Additionally, there is a high incidence of self-reported physical or sexual abuse and early childhood trauma among persons with chronic pain,[66] making psychiatric problems the most prevalent comorbidity in these patients.[67,68] There is a well-established relationship between increased self-reported emotional distress and increased pain sensitivity and pain-related disability.[68,69] An analysis of large insurance claims data performed by PharmMetrics of 36 million patients from 61 health plans comparing patients with anxiety and depression with matched controls found that those who had evidence of negative affect (high anxiety and depression) had more somatic complaints, more pain, and had greater utilization of medical services.[70]

Opioid Therapy and Mood Disorder

In an earlier survey study conducted by Arkinstall and colleagues, patients prescribed opioids were found to have a 50% prevalence of a mood disorder.[71] Grattan and others reported that it was more likely that patients would be prescribed opioids for their mood disorder and affective distress than their reported pain severity or physical pathology.[65]

Several studies have demonstrated that persons with chronic pain with significant psychopathology tend to demonstrate poorer outcomes than those with minimal psychopathology. These individuals

report greater pain intensity and more pain-related disability.[72,73] Elevated anxiety and depression are common among chronic pain patients, and having a mood disorder is correlated with poor rates of return-to-work.[74] In a blinded controlled trial examining the benefits of IV morphine compared with saline among chronic pain patients, those individuals who demonstrated higher levels of psychopathology reported the least reduction of pain when administered IV morphine.[72] Thus there is consistent evidence that individuals with chronic pain and significant negative affect benefit less from opioids and many other treatments designed to control their pain.[50,67]

Studies have found that individuals with chronic pain and high rates of emotional distress and negative affect are much more likely to misuse opioid medications.[65,75,76] There is some indication that certain patients use prescription opioids to help reduce their anxiety and depression.[74] Although many patients with emotional distress and a mood disorder also have a substance use disorder, a study among chronic pain patients without a history of substance abuse showed that having increased anxiety and depression increased the incidence of opioid misuse.[59,77] Taken together, there is evidence that attempts at reducing affective distress can cause reduced risk of substance abuse.[58]

Risk Assessment Tools

With recent attention to the "opioid crisis," healthcare providers have been challenged with the need to provide appropriate relief from pain while avoiding risks associated with the use of opioids. This has contributed to a greater need to employ risk assessment measures to identify those who are more predisposed to misuse of prescription opioids.[40,41] Guidelines from healthcare organizations and regulatory institutions have strongly encouraged the use of risk assessment screening tools.[78,79] Stressed within these guidelines is the importance of thoroughly evaluating all potential users of prescription opioids by conducting a complete social and medical history, with a medical examination and a review of medical records.

There are several validated and reliable self-report screenings that can help to assess the risk of opioid misuse. Unfortunately, many of the recommended ways to assess substance use disorders and alcohol dependence, particularly through the criteria outlined in the DSM, fifth edition (DSM-V), have not been validated with chronic pain patients.[80] These measures tend to use signs of opioid dependence and tolerance as indicators of abuse and addiction when no abuse exists.

Over the years, several screening measures have been developed that have been shown to be particularly useful in assessing the risk of prescription opioid abuse among persons with chronic pain. These include the Screener and Opioid Assessment for Patients with Pain—Revised (SOAPP-R),[81–83] that is a trait measure of abuse risk. Shorter versions of this measure[84–86] and a Spanish translation exist.[87] A sister questionnaire that assesses states of abuse risk (e.g. can change over time) is the Current Opioid Misuse Measure (COMM).[88,89] Both the SOAPP-R and COMM have been cross-validated and used extensively in clinics and research protocols.[90,91] A shortened version of the COMM also exists.[92] Other self-report questionnaires include the Opioid Risk Tool (ORT),[93,94] the Diagnosis, Intractability, Risk, and Efficacy (DIRE) scale,[95] the Drug Use Disorders Identification Test (DUDIT),[96] the Drug Abuse Screening Test (DAST),[97,98] the Screening Instrument for Substance Abuse Potential (SISAP),[99] the Pain Medication Questionnaire (PMQ),[100] and a single item of catastrophizing that is useful in predicting opioid misuse among chronic pain patients.[101] A systematic review by Lawrence and colleagues (2017) found the SOAPP-R, COMM, and PMQ to be most valid to assess the risk of problematic analgesic use among patients with chronic pain.[102] The ORT has been popular because of its brevity (five items), and a revised ORT that omitted the question about prior childhood sexual abuse now finds comparable opioid risk between men and women.[103] A brief checklist designed to reflect the content of a standard opioid agreement (opioid compliance checklist, OCC) has also been validated and used clinically.[10,25]

Although there are weaknesses with using any self-report measure of opioid risk, and it is always possible to under report problems, these validated self-report screening tools are one of several ways to gain some understanding of the chronic pain patient and help identify those with a predisposition for opioid misuse. It is important to state that while higher scores on these measures may not eliminate the option of prescribing opioids, they may draw attention to the need for more careful tracking and monitoring of certain individuals.[102] Brief descriptions of these assessments and other tools are provided in Table 51.3.

Strategies for Managing High Risk Patients

Practice Guidelines

Treatment approaches are needed that balance the proper treatment of chronic pain while minimizing the risks associated with opioid use. There has been a dramatic increase in the use of opioids for non-cancer pain over the past few decades, and guidelines from the CDC and elsewhere have been published about the steps needed to reduce abuse, diversion, and addiction as a result of prescription opioids.[104,105] These guidelines strongly recommend using validated screening instruments designed to identify individuals at higher risk of opioid misuse in clinical practice. The goal of these screening instruments is to reduce the risk of iatrogenic addiction. Risk assessment should be combined with a review of past medical records and a thorough history and physical examination—since each assessment process alone may not be accurate in identifying those individuals who are not suitable candidates for opioids or who might need very careful monitoring. Initial screening should also include the history of and current comorbidity of substance abuse. Urine toxicology screening is recommended, and the monitoring of prescribed opioids through a prescription drug monitoring program (PDMP). In addition, opioid therapy agreements and the practice of universal precautions are highly recommended.[106,107] Together, these combined strategies help to reliably stratify risk levels and help tailor treatments to match this risk. There has been a recent trend to prescribe lower daily doses of opioids over a shorter period,[108] although a recent systematic review suggests that prescribing higher doses of stronger opioids does not always predict increased incidence of opioid dependence and abuse.[36]

Urine Toxicology Screening

The use of urine toxicology screens to establish prescription opioid compliance is well documented.[109] Most hospital-based toxicology screens use immunoassay to determine the presence or absence of a class of drug in the urine sample. The use of gas chromatology/mass spectrometry (GCMS) allows the determination of the quantity of each drug present. GCMS offers a test of creatinine levels to determine possible tapering and establishing the absence

TABLE 51.3 Opioid and Medication Abuse Screening Assessments

Name of Questionnaire	References	Purpose of Questionnaire
Current Opioid Misuse Measure (COMM)	Butler et al. 2007; 2010; McCaffrey, 2019[88,89,92]	Seventeen item self-report assessment developed for identifying chronic pain patients who are currently misusing prescription opioids. The opioid risk cutoff score is nine. The reliability and predictive validity of the COMM were found to be highly significant. A shorter version has been developed and validated.
Diagnosis, Intractability, Risk, and Efficacy (DIRE)	Belgrade et al. 2006[95]	Predicts the feasibility of long term opioid treatment for non-cancer pain. Also used to pinpoint beneficial factors, if any, of an individual's opioid use. The opioid risk cutoff score is 14.
Drug Abuse Screening Test (DAST-2)	Tiet, 2017; Giguere, 2017[97,98]	Two item version of the longer DAST to assess evidence of substance use disorders. This test has not been validated for chronic pain patients.
Drug Use Disorders Identification Test (DUDIT)	Hildebrand, 2015[96]	Eleven item drug use disorders assessment tool that was developed for those exposed to opioid analgesic therapy. This was not initially developed for persons with chronic pain.
Opioid Compliance Checklist (OCC)	Jamison et al. 2014; 2016[10,25]	Twelve item questionnaire developed to assess compliance for chronic pain patients on long term prescription opioids. Five items were found to best predict subsequent aberrant behaviors based on multivariate logistic regression analyses.
Opioid Risk Tool (ORT)	Webster and Webster, 2005; Webster and Dove, 2007; Cheatle et al. 2019[93,94,103]	Five item checklist that allows the physician to determine if a patient will display aberrant drug-related behaviors. The opioid risk cutoff score is eight. An updated version without a history of childhood sexual abuse has been validated.
Pain Assessment and Documentation Tool (PADT)	Passik et al. 2004[137]	Forty-one item questionnaire that provides extensive documentation of the patient's progress and objectively monitors a patient's care. There is no numeric scoring method for this assessment.
Pain Catastrophizing Item	Lutz, 2017[101]	One item from the coping strategies questionnaire assessing catastrophizing that is shown to predict the risk of opioid misuse. It is highly correlated with the SOAPP-R.
Prescription Medication Questionnaire (PMQ)	Holmes, 2006[100]	A self-report questionnaire designed to assess risk for opioid medication misuse among chronic pain patients.
Prescription Drug Use Questionnaire (PDUQ)	Compton et al. 2008[116]	Forty-two item questionnaire used to identify subjects who are likely to be nonaddicted, substance abusing, or substance-dependent.
11. Screening Assessment for Substance Abuse Potential (SISAP)	Coambs et al. 1996[99]	Five item self-report screening questionnaire for substance abuse potential catered mostly toward alcohol abuse.
12. Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)	Butler et al. 2004; Butler et al. 2008; Butler et al. 2009; Butler et al. 2013; Finkelman et al. 2015, 2017; Black et al. 2018[81–87]	Twenty-four item self-administered screening tool designed to predict aberrant medication-related behaviors for chronic pain patients being considered for long term opioid therapy. The opioid risk cutoff score is 18. The reliability and predictive validity of the SOAPP-R were found to be highly significant. Shorter versions have been developed and validated.

of prescribed opioids or the presence of nonprescribed or illicit substances.[110] Providers rely on regular urine toxicology screenings as an objective way to assess compliance. Over time, despite their limitations, these tests have become more accurate with fewer false positives.[109,111] For those prescribed opioids for pain who are perceived to be at lower risk of opioid misuse, a toxicology screening at least once a year is recommended. More frequent screens are recommended for those who are identified as at higher risk of opioid misuse.[112]

In a study of 226 patients with chronic pain, 46.5% of these patients prescribed opioids for pain showed evidence of an abnormal urine toxicology screen, which underscores the importance of urine screens.[113] Many clinics use immunoassay urine screens as the first line of analysis, followed by the completion of GCMS testing when it is important to detect the specific level of drug metabolite in the urine. Because random urine toxicology screening has revealed a high incidence of abnormality, the use of self-report measures of risk alone may not be optimal, and a combination of urine toxicology screens, opioid checklists, and tracking the PDMP would be optimal.

Prescription Drug Monitoring Program

There has been an increased focus on government and regulatory action to help reduce opioid abuse and diversion. One instituted state-wide initiative has been PDMPs. This effort was designed to analyze and monitor electronic prescription data primarily from pharmacies. There has been a gradual increase in the use of PDMP

data among states.[3] The goal is to obtain reliable data collection of opioid use to help identify the use of prescription opioids.

Opioid Therapy Agreements

Specialty pain clinics have used opioid therapy agreements for many years to inform patients who are prescribed opioids for pain about the expectations and the proper use of opioids. These agreements are designed to inform the patients of potential risks with opioid use and to improve patient compliance with opioid medication.[106,114] These agreements serve to educate the patients in their need to be responsible with their use of prescription opioids and to document the risks associated with misuse. By agreeing to the expectations of use, the providers and patients can acknowledge in writing what would be expected of all the parties for adherence to opioid use. Although the evidence is weak that opioid therapy agreements improve adherence, they are universally recommended.

In most opioid therapy agreements, there are conditions required of the patient to remain on opioid therapy. Although not a legal document, the patients are made aware of potential risks and adverse effects associated with opioid use.[10,25] Typically, patients are informed that they should use the medication only as prescribed, that they should receive opioid medication only from one provider and one pharmacy, that they will not be given extra medication if they run out early over the designated time of the prescription, and additional medication will not be substituted if lost or stolen. They also agree to periodic urine toxicology screens and to be responsible for keeping their clinic appointments. If, as perceived by the prescribing physician, it is determined that the risk of opioid therapy outweigh the benefits, then a gradual tapering of the opioids would take place.[3,53]

It is important to review each component of the agreement with the patient and to have a signed copy saved in the electronic medical record. Clarification of all components of the agreement is important so that all parties are aware of what is expected. Signing the agreement and distributing copies to all involved helps to acknowledge the conditions and responsibilities set by the clinic. It is recommended that this agreement be read and signed each year that opioids are being prescribed for pain. This will serve to remind the persons with pain of their responsibilities for using prescription opioids and the need to be very careful with these substances. Additionally, patients should be reminded periodically that violation of the agreement could result in a gradual discontinuation of the opioids. The opioid compliance checklist is an eight item checklist that is administered monthly to those prescribed opioids for pain and was created based on a typical opioid agreement.[10,25] It serves to document adherence of the opioid users. The responsibility of maintaining compliance with opioids is up to the patients receiving this medication, but physicians should remain vigilant in tracking compliance and verifying adherence.[3] Unfortunately, the evidence in support of the effectiveness of opioid therapy agreements in reducing opioid misuse and abuse has been weak, but their use is very much encouraged in opioid therapy guidelines.[115]

Behavioral Strategies to Improve Opioid Treatment Adherence

Providers are often conflicted about ways to best manage chronic pain patients who have clear pathology to account for their pain but who also are at high risk for opioid misuse. Many choose to avoid the use of prescription opioids altogether. If the need arises to consider opioid therapy for individuals who have predisposing factors for opioid misuse (e.g. postoperative pain; see Table 51.2), certain strategies may be needed to help increase opioid compliance and avoid opioid abuse. In a randomized trial, high risk patients with primary lower back pain either received interventions to assist with improving opioid compliance or were assigned to a treatment as the usual control condition. A low risk patient group was also recruited. All subjects were followed for six months. Those in the high risk experimental group were asked to give a urine toxicology screen at each monthly appointment, complete an opioid compliance checklist, attend individual cognitive behavior motivational counseling, and participate in monthly group sessions designed to address ways to avoid opioid misuse.[53] Subjects who admitted to opioid misuse on the prescription drug use questionnaire (PDUQ),[116] who had abnormal urine, or who showed a positive score on the physician-rated addiction behavior checklist (ABC)[117] were classified as positive on the opioid misuse index (OMI). Results showed that those high risk subjects who were carefully monitored and who received motivational counseling showed significantly lower opioid misuse indexes than the high risk controls and, in fact, had as low an indication of opioid abuse as those designated as low risk subjects. These findings suggest that risk assessment and careful monitoring with cognitive behavior support can significantly improve opioid compliance and adherence.

It has now been recommended that anyone prescribed opioids for pain should be administered a comprehensive assessment. This would include a self-report questionnaire and a detailed history and physical. All patients should read and sign an opioid agreement and be monitored based on their level of risk. However, for those at greatest risk for opioid misuse, a lower dose of prescription opioids, regular urine screens, completion of an opioid compliance checklist, and motivational counseling would be recommended. Some providers encourage the use of pill counts.[3] The ultimate result is that with careful monitoring and risk assessment, the opportunities for opioid misuse will be mitigated.[46]

Future Considerations

Newer opioid analgesics have been recently developed with the goal of deterring abuse. These so-called abuse-deterrent opioids intend to prevent abusers from injecting, crushing, snorting, and otherwise altering long-active opioid formulas.[118,119] The goal is to create safe opioids to be used by patients while making them unattractive to those who want to use the opioids for purposes leading to euphoria. Different formulations have been developed that combine the opioid with an antagonist that is released when the drug is compromised.[120,121] There is evidence that abuse-deterrent opioids have decreased the incidence of prescription opioid abuse in long-acting opioids.[122,123]

Innovative technology has been used to track opioid compliance and to educate pharmacists and physicians, which will continue to be developed. Containers and patient-specific serialized blister-packaging of opioids can be electronically monitored along with the date and time a medication is taken. There has been a rapid growth of mobile phone applications (apps) in pain assessment and management.[124–126] The advent of mHealth (mobile health) technology using short messaging service and activity monitors has promoted ways for patients to communicate with healthcare providers and track activity between clinic visits.[124,127] Not only is this technology useful in collecting information in

clinical trials, but clinics can use this information to help document outcome and compliance. Currently, 95% of the world population has access to the internet, and remote tracking and monitoring are much more accessible to patients worldwide. There is a broadening of access to information and personal health data, which can improve coping and potentially reduce healthcare utilization. There is a call for better pain education among providers,[47] increased use of social media, incorporation of online peer education, and daily support to chronic pain patients on opioid therapy.[128–130] The future will likely include the use of artificial intelligence to identify those individual characteristics to help predict the optimal outcome from opioid therapy.[130,131]

Future identification of markers for opioid benefit and abuse within endogenous chemical reactive systems will shed light on our understanding of tolerance, OIH, craving, and potential opioid misuse.[132] Longitudinal studies investigating demographic variables or gender, ethnic origin, and personality characteristics will help in creating empirically based practice guidelines. Nanotechnology is used to deliver treatment to a specific targeted area, and the development of other delivery strategies like topical preparations will add to the treatment armamentarium. Increased understanding of how acute pain develops into a chronic pain condition will aid in identifying those at risk for developing chronic pain. Increasing the use of genome research and genetics testing to help identify markers for potential opioid abuse will make a positive impact on opioid risk assessment.[133,134] There has been a recent emphasis on the use of behavioral interventions such as mindfulness to reduce craving and improve coping.[135,136] The overall reduction of suffering related to chronic pain would be the long-range goal, and increased understanding of the mechanisms contributing to pain would be what is most hoped for in the future.

Summary and Conclusions

Chronic pain is a global health problem that exacts enormous costs both in terms of money spent treating pain and lost productivity because of pain. Chronic pain inflicts an enormous human toll of suffering and disability and is often associated with psychiatric comorbidities such as emotional distress, negative affect, depression, and anxiety. There is a corresponding relationship between mood disorder and opioid misuse, abuse, and/or diversion. There has been an opioid epidemic because of lax opioid prescribing practices in the past. The future of opioid prescribing calls for careful monitoring and risk assessment, opioid therapy agreements, urine toxicology screens, the use of PDMPs, and behavioral interventions designed to improve opioid compliance. There is a role for innovative technology to help healthcare providers manage chronic pain patients who are prescribed opioids for pain. Support is critically needed for future controlled trials to help in our understanding of the best ways to offer and manage chronic opioid therapy. Continued sponsorship of research to advance our empirical understanding of the use of opioids for pain is critically needed.

Key Points

- Chronic pain inflicts an enormous human toll of suffering and disability and is often associated with psychiatric comorbidities such as emotional distress, negative affect, depression, and anxiety.
- There is a corresponding relationship between mood disorder and opioid misuse, abuse, and/or diversion.
- Because of suboptimal opioid prescribing practices in the past, there has been an opioid epidemic, and the future of opioid prescribing calls for careful monitoring and risk assessment.
- There are several validated and reliable self-report screenings that can help to assess the risk of opioid misuse.
- Opioid therapy agreements, urine toxicology screens, the use of PDMPs, and behavioral interventions are designed to improve opioid compliance.

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Pain and Addictive Disorders: Challenge and Opportunity

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Introduction

The treatment of pain in patients with comorbid addiction or substance use disorders (SUDs) is complex.[1] Traditionally, chronic pain and SUDs have been treated by separate providers in different clinical settings. Until recently, pain researchers routinely excluded individuals with SUDs from clinical trials of treatments for chronic pain. Since chronic pain and SUDs frequently co-occur, pain management specialists must be able to recognize these interrelated chronic relapsing medical conditions in the patients they are evaluating and incorporate appropriate treatment strategies for these patients. This chapter aims to provide pain providers with an up-to-date overview of research related to pain management in patients with SUDs. We focus most on opioid use disorder (OUD) because this is the most commonly examined SUD in pain management literature. After reviewing the nomenclature, the SUD diagnostic criteria, and the neurobiology of addiction, we discuss the prevalence and causes of comorbid pain and SUDs and the challenges of treating pain in this population, including patient clinical complexity and changing perspectives on the role of prescription opioid analgesics and non-opioid treatments. We review the screening, monitoring, and management of SUDs in patients with chronic pain and approaches to treat chronic and acute pain in patients with SUD, with a particular focus on cannabis use disorder and OUD. Throughout, we discuss the importance of collaboration between pain specialists and addiction clinicians and the essential role that pain providers play in treating patients with SUDs.

Nomenclature

To promote a common taxonomy, the Board of Directors of the American Society of Addiction Medicine (ASAM) in December 2019, adopted the following definition: "Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences."[1] We draw the reader's attention to three often overlooked implications of this definition: (1) addiction is a chronic relapsing medical condition or disease similar to diabetes or hypertension[2]; consequently, providers should expect patients with addiction to be symptomatic periodically, and providers should not automatically discharge patients from treatment for being symptomatic, (2) addictions are treatable; effective treatments for SUDs (i.e. those which attenuate substance use and reduce risk of overdose, infectious disease, and all-cause mortality) vary by the nature of the substance used; in the cases of addiction to alcohol, nicotine, or opioids, effective treatment often consists of a combination of Food and Drug Administration (FDA)-approved medications and counseling to facilitate lifestyle changes,[3–6] and (3) the rates of success of addiction treatment are comparable to those for other chronic medical conditions.[2] For example, the median 12 month medication adherence in a meta-analysis of patients receiving medication for OUD was 57% globally.[7] In comparison, the mean medication adherence was 59% across studies in a meta-analysis of medication adherence in patients receiving antihypertensives, lipid-lowering agents, and oral anti-diabetics.[8]

The ASAM definition stands in stark contrast to common societal misconceptions that addiction is an acute condition because of a "moral defect" or character flaw.[9–11] Since providers and patients may be influenced by such inaccuracies, clinicians need to be aware of their own assumptions (and possible biases) concerning SUDs and the people who have them.[12] Language is one way that biases are manifested. Certain words or terms used by providers (and researchers) may promote stigma among patients. Consequently, in recent years, increased attention in addiction medicine scholarship and clinical practice has focused on using neutral and person-first terminology to avoid stigmatizing individuals (e.g. "person with a SUD" rather than "addict") and to reinforce that SUDs are medical conditions.[13–15] A recent paper suggests that medical students are still being exposed to pejorative terminology about SUDs in their materials when studying for the United States medical licensing examination.[16] It is notable that government agencies and the legal system have historically used derogative language when describing addictions or the people who have them. For example, the Controlled Substances Act defines an "addict" as a person who "habitually uses any narcotic drug to endanger the public morals, health, safety, or who is so far addicted to the use of narcotic drugs as to have lost the power of self-control regarding his addiction."[17]

[1]The terms substance use disorders and addiction are used interchangeably in this chapter.

Provider language may be particularly important because patients with chronic pain and/or SUDs experience stigma and discrimination within the healthcare system, which in turn reduces treatment-seeking and the likelihood of disclosing substance use.[12,18] Multiple studies have demonstrated that physicians underestimate pain among Black and Hispanic patients and that such patients are less likely than White patients to receive analgesia in acute pain settings.[19] Providers may screen Black pain patients for drug use more than White patients and are more likely to discontinue treatment for Black patients if their drug screens are positive.[20] However, Black patients are less likely than White patients to be referred for specialty pain management.[21] Research also shows that social determinants of health, including education and wealth, might play a role in pain prevalence and severity, with patients with less wealth and lower education experiencing more and higher severity pain.[22] Consequently, it is important for providers to solicit their patients' experiences of pain and SUDs and engage in patient-centered shared decision making regarding treatment plans. We recommend that providers standardize screening and monitoring practices for patients, regardless of patient demographics (see the section on screening instruments).[20,21]

While SUDs are associated with brain and other biologic changes (see the section on neurobiology), diagnoses are based on behavioral patterns and patient reports. In the United States, providers use the *Diagnostic and Statistical Manual, fifth edition (DSM-5)* to diagnose SUDs.[23] The DSM-5 criteria for "substance use disorder" require a maladaptive pattern of substance use leading to significant impairment or distress, as manifested by at least two of the following, occurring within a 12 month period (criteria have been abbreviated)[23]:

1. The substance is often taken in larger amounts or over a longer period than intended
2. There is a persistent desire or unsuccessful effort to cut down or control substance use
3. A great deal of time is spent on the activities necessary to obtain or use the substance or recover from its effects
4. Craving or a strong desire or urge to use the substance
5. Recurrent use of the substance results in failure to fulfill major role obligations
6. Use of the substance is continued despite causing or exacerbating persistent or recurrent social or interpersonal problems
7. Important social, occupational, or recreational activities are reduced because of substance use
8. Substance use occurs in situations in which it is physically hazardous
9. Continued substance use despite the knowledge that it has caused or exacerbated ongoing or recurrent physical or psychological problems
10. Tolerance[2]
11. Withdrawal[2]

The DSM-5 also includes one "non-substance-related disorder" under its classification of "addictive disorders": gambling disorder.[23] Anecdotally, we have heard that patients describe gambling or gaming as an activity that takes their focus off of pain, and the co-occurrence of gambling disorder and chronic pain is understudied.[24–25]

[2]As outlined in the next section, which includes a description of tolerance and withdrawal, neither of these criteria are considered to have been met for individuals taking opioids solely under appropriate medical supervision.

Terms Related to the Treatment of Opioid Use Disorder

The FDA has approved three medications for the treatment of OUD: methadone (full agonist), buprenorphine (partial agonist), and naltrexone (antagonist). Collectively, they were referred to as "medication-assisted treatment." The preferred nomenclature is currently "medications for OUD," in part to emphasize the central (and not secondary) role of the medications.[26] See the section titled "Medications for Opioid Use Disorder" for more information. Opioid agonist treatment refers to the treatment of OUD involving either methadone or buprenorphine.

Neurobiology of Addiction

Over the past several decades, basic and clinical research has uncovered neuroscientific explanations of SUDs. These explanations challenge stereotypes that invoke moral weakness as a reason for drug addiction and instead provide scientific reasons for addiction, offering guideposts to treatment-seeking patients and their doctors.

Addictive substances, including opioids, cocaine, amphetamine, ketamine, nicotine, and marijuana, exert powerful effects on dopaminergic neurons, which produce euphoric states exceeding what is typically produced by endogenous levels of dopamine. These sharp increases in feelings of reward can be associated with the environmental stimuli that surround drug use. With chronic drug exposure, wear and tear on dopaminergic neurons begin to suppress the experience of reward itself, which in turn drives craving, anticipation, and the need for more drugs to satisfy drug urges.[11,27] Notably, individuals with addiction are frequently confused by their ongoing use of drugs that no longer provide pleasure. Addiction can then be understood as a motivational push to avoid the discomfort associated with dysregulated reward circuity and the distress caused by feelings of being without sufficiently numbing, activating, or altering drugs.[11,27]

In the last decade, a useful heuristic has been developed that delineates the neuroanatomy, circuits, and signaling molecules involved in the cycle of addiction from stages of binge/intoxication to withdrawal/negative affect to preoccupation/anticipation. The delineation of these separable, tractable circuits and the signaling molecules involved establishes a framework for researchers to identify therapeutic targets, potential medications, validated animal models, and clinical trials to test new pharmacologic interventions based on rational therapeutic targets.[11,27] This heuristic has had critical epistemologic value for the field researchers, clinicians, and patients—and is worth reviewing here.

In the binge/intoxication phase of addiction, drug use is motivated primarily by positive, rewarding experiences subserved by the ventral and dorsal striatum, globus pallidus, and thalamus. Illicit drugs powerfully activate neurons in these brain regions with no connection to purposeful behavior. This overstimulation leads to progressive and insidious dysregulation of the brain's natural reward mechanisms. Over time, there is a downregulation of positive reward pathways, and increasing drug levels are needed to trigger the brain reward system. Animal and human studies have shown that long term exposure to drugs of abuse impairs dopamine neurons and dopamine signaling in the nucleus accumbens. This effect appears to be mediated by the actual physical shrinkage of dopamine neurons in response to chronic drug administration.[28] This underlying neuroanatomic change reduces the capacity for reward and leaves the addict "unrewarded," amotivational, and often depressed in the absence of a drug. Research has shown that

drugs of abuse decrease the size of dopamine neurons in the ventral tegmentum and nucleus accumbens by depriving the neurons of the crucial nerve growth factor, brain-derived neurotrophic factor.[28] What started off as euphoria in response to unanticipated reward turns over time into overwhelming behavior-modifying drug craving.

During the withdrawal-negative-affect stage, the dopamine systems are compromised, contributing to dysphoric mood states while simultaneously assigning greater salience to drugs and drug related stimuli in the context of these aversive states, and healthy rewards lose motivational power as they fail to satisfy. Drug consumption triggers much smaller increases in dopamine levels in the presence of addiction (in both animals and humans). Over time, the attenuated release of dopamine renders the brain's reward system much less sensitive to stimulation by both drug related and non drug related rewards. Individuals with addictions often seek a more potent release of dopamine in more explicitly risky settings. The human costs to relationships, community, and vocation increase as the drug produces less euphoria. Adaptations in the circuitry of the extended amygdala in the basal forebrain lead to the emergence of negative emotions.

During the *preoccupation-anticipation* stage, those with addiction desire and pursue drug use. This stage of the addiction cycle is characterized by chronic relapse frequently triggered by the long term effects of drugs of abuse on the basolateral amygdala, hippocampus, and prefrontal cortex.[11,27] Notably, the hippocampus is a target of opioid receptor agonists, such as morphine, methadone, heroin, and various short-acting opiates.[29] The opioid system within the hippocampus underlies context-associative learning, which is essential for linking drugs with a particular place and set of events.[30] In addition, chronic drug use impairs the prefrontal cortex and the capacity for self-regulation, decision making, and flexibility.[11] Together, these combined effects in the amygdala, hippocampus, and prefrontal cortex explain how earnest plans to cease substance use are upended by desire, environmental context, and impulsivity.

Finally, in addition to direct brain effects of drugs of abuse, considerable evidence from population-based studies supports a positive association between psychosocial adversity, chronic distress, and addiction.[31] The contribution of stressors to substance use appeared to occur in a dose-dependent manner. Repeated or chronic prolonged stress can induce lasting changes in stress responsivity and the magnitude and duration of stress hormone response to a stressor, which in turn increases the risk of stress-related disorders and addiction.[31] Similar to drugs of abuse, stress exposure increases dopamine release in the nucleus accumbens. Given that both drugs of abuse and stress activate mesolimbic pathways, each results in synaptic adaptations in the ventral tegmental area dopamine neurons and the prefrontal cortex. While persistent and poorly controlled responses to environmental challenges contribute to the persistence of and relapse to self-administration of drugs of abuse and addiction, it is clear that vulnerability to drug use and relapse may exist prior to the use of addictive drugs on a genetic or acquired basis-histories of childhood neglect and abuse, for example, may lead to the acquisition of addiction because of underlying baseline differences in stress responsivity.[29,31,32]

Misconceptions About Physical Dependence and Addiction

Many persons with SUDs report that compared with their first use, they increased the amount of the substance over time to obtain the same effect, or that the amount of the substance used to produce the effect no longer does (i.e. tolerance). They also may report that upon abrupt cessation of substance use, their bodies exhibit a characteristic pattern of symptoms (i.e. withdrawal). Withdrawal symptoms vary according to the category of substances involved (e.g. alcohol and opioids). According to the DSM-5, an individual who takes the substance (or a similar substance) to relieve or avoid withdrawal symptoms is also considered to have met the criterion for withdrawal. Depending on the severity of the addiction and the type of substance, withdrawal symptoms can range from relatively mild (e.g. headache because of caffeine withdrawal) to life-threatening (e.g. seizures because of alcohol withdrawal). However, the presence of tolerance or withdrawal, which are hallmarks of physical dependence, is not associated with the presence of a SUD. Tolerance and withdrawal are related to pharmacologic properties. Both tolerance and withdrawal can occur when patients take prescription medications as prescribed (e.g. anti-depressants and anxiolytics). Consequently, the DSM-5 specifies that for those prescribed opioid analgesics and who take them as prescribed (in the absence of other illicit opioid use), tolerance and withdrawal should not be counted toward the number of criteria needed to meet the diagnostic threshold for OUD.

Prevalence of Substance Use and SUDs Among Those With Chronic Pain

The estimated prevalence of SUDs among those with chronic pain ranges from 1%–40%. Reasons for this variability in estimates include study differences in time frames (e.g. current vs. lifetime), assessment methods (e.g. screening versus diagnostic assessment), and populations (e.g. in treatment vs. not in treatment).[33] Nevertheless, it is clear that a sizable proportion of patients with chronic pain, including those receiving long term opioid therapy (LTOT), have comorbid SUDs.[34] In 2019, an estimated 5.3% of the United States population aged 12 years or older had an alcohol use disorder, while an estimated 3.0% had an illicit SUD.[35]

Opioids

A systematic review estimated that 8%–12% of those on LTOT met the criteria for OUD and 21%–29% met criteria for "opioid misuse."[36] Conversely, the rate of chronic pain among patients with OUD entering opioid agonist treatment is high, with estimates varying between 37% and 61% who report chronic pain.[37–43]

Tobacco

Tobacco use is common among those with chronic pain, with prevalence estimates as high as 50% (twice that of the general population).[44–46] Relatedly, nearly 60% of individuals with tobacco use disorder also experience chronic pain. In a nationally representative sample of 9,282 United States adults, respondents with lifetime chronic neck or back pain were 1.3 times more likely to smoke cigarettes than the general population, 1.8 times more likely to be diagnosed with a lifetime nicotine use disorder, and 2.4 times more likely to meet the criteria for past year nicotine use disorder.[46] Previous research supports the theory that pain may contribute to the development of tobacco use problems,[44] and that tobacco use, in turn, may contribute to the development of painful conditions such as back pain[47] or rheumatoid arthritis.[48]

Cannabis

Approximately 36% of those on LTOT report cannabis use,[49] while as many as 15% of primary care patients report past 30 day cannabis use.[33] Because of the rapidly expanding legalization and availability

of cannabis, cannabis use disorder (CUD) is increasingly common in the general population,[50] although the prevalence of CUD among those with chronic non-cancer pain has been understudied. One study identified that the rate of CUD in patients hospitalized for chronic pain increased from 1.9% in 2011 to 3.0% in 2015.[51]

Alcohol and Sedatives

An estimated 25% of patients seeking treatment for pain report moderate to heavy alcohol use.[52] In the general population, those with chronic neck or back pain compared to those without are nearly twice as likely to meet the criteria for alcohol use disorder.[53] Alcohol has been linked to worse pain outcomes, such as increased pain disability and intensity. An estimated 9%–11% of those with chronic pain who are treated in a primary care setting meet the criteria for a sedative use disorder.[54,55]

Stimulants

Chronic pain may be associated with an increased risk of stimulant use. Among a national sample of adults, stimulant use was almost twice as prevalent among those with versus those without chronic low back pain (cocaine: 22% vs. 14%; methamphetamine: 9% vs. 5%).[56] A prior study of attendees at an outpatient pain management clinic estimated that the rates of cocaine and methamphetamine use were 5% and 2.5%.[57] Importantly, stimulants and opioids influence dopaminergic receptors in the central nervous system either by activating the dopamine receptors directly or by way of the opioid receptors.[58] For this reason, there is an enhanced risk of addiction and adverse events among those who concurrently use stimulants and opioids.

Chronic Pain Among Patients With SUDs

A recent study of participants in a large academic healthcare system found that most of those with SUD had chronic pain (opioid, 75%; cannabis, 64%; alcohol, 59%; tobacco, 60%).[59] Other studies have found that patients receiving opioid agonist treatment with co-occurring chronic pain frequently report using tobacco and alcohol as well as non-medical use of cannabis, opioids, and benzodiazepines to manage pain.[37,38] Given the extent of the co-prevalence of chronic pain and addiction, it behooves pain providers and addiction providers to be knowledgeable about both chronic medical conditions.

Complexity and Confounds

The presence of either chronic pain or SUD can obscure the diagnosis and treatment of the other.[60] In SUD treatment settings, chronic pain is not routinely assessed or addressed, while the reverse holds for pain management settings. For some individuals with chronic pain and SUDs, chronic pain precedes the onset of SUD. For others, SUD precedes or occurs at approximately the same time as the onset of chronic pain.[61,62] The order of onset may have implications for how patients self-identify (e.g. a woman whose pain occurred first and who reported developing an addiction to opioids that were prescribed for pain relief may view herself as a "pain patient" and downplay the presence of SUD). Although this field of research is nascent, one study found that among 170 patients seeking treatment for co-occurring chronic pain and OUD, those whose chronic pain preceded OUD were less likely to meet the criteria for a current non-opioid SUD compared to those whose OUD occurred first.[63]

Individuals with SUDs have high rates of medical problems, including trauma related to physical and sexual assault,[64] and painful illnesses such as cirrhosis, hepatitis C, and HIV.[65–67] Accidents (e.g. motor vehicles) are among the most frequently reported causes of chronic pain among patients receiving opioid agonist treatment.[68] Conversely, having pain increases the likelihood of exposure to controlled substances.[60] High rates of psychiatric disorders, including anxiety, mood, and personality disorders, are accompanied by chronic pain, especially among those with OUD.[69–71] We note that among patients on LTOT, psychiatric disorders are associated with higher opioid doses and a higher risk of accidental overdose.[72] Given the reliance on self-report in the assessment of pain, patients with SUDs seeking opioids for the management of chronic pain may be unintentionally motivated to de-emphasize the effects non-opioid therapies may have on their pain.[60] Conversely, increased focus in recent years on opioid-related harms may have dissuaded some patients on opioid agonist treatment to seek or take opioid analgesics in cases where it might be appropriate (e.g. prescribed by an emergency department provider to manage pain following a serious motor vehicle accident).

Comorbid addiction complicates the treatment of pain in numerous ways. Patients may rely on the use of substances for analgesic and mood-enhancing properties and are more susceptible to worse pain outcomes.[73] Those with comorbid addiction and pain are also at higher risk of adverse outcomes to opioid medications, including overdose and death.[72] Consequently, pain clinicians should screen for addiction risk before and during treatments, especially for treatments involving controlled substances, and they should be prepared to either provide treatment for SUDs or offer treatment referrals.

Universal Precautions

Screening tools for SUDs can be viewed as part of universal precautions in the treatment of pain, irrespective of the proposed pain intervention. Providers can check their state's electronic prescription drug monitoring program; these data can be compared to the information provided by the patient. Patients' relatives or significant others can also be important sources of collateral information.

Gourlay and Heit developed guidelines for universal precaution guidelines for pain management comparable to those used for infection control.[74] We suggest a modified version of these guidelines that concurs with the 2016 Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids to patients with chronic non-cancer pain (Box 52.1).[75] The original Gourlay and Heit step six, which assumed that opioids were appropriate as a first line pain management intervention for many patients with non-cancer chronic pain, has been revised in our modified version: "Initiate pain management intervention." According to the CDC guidelines, for the modified step six, clinicians should consider non-opioid pharmacotherapies and evidence-based non-pharmacologic pain management interventions as first line treatment (see Chapters 34, 37 for treatment of neuropathic and chronic widespread pain; Chapters 53, 54, and 55 for non-opioid medications; and Chapters 58–61 for non-pharmacologic interventions) (Box 52.1).

Substance Use Disorder Screeners

Since the rates of SUDs are high in persons with chronic pain, pain management providers should consider assessing for SUDs, regardless of the provision of opioid analgesics. We review below some common SUD screeners. If patients screen positive, they should be further assessed for DSM-5 SUDs.[23]

• BOX 52.1 The Modified Ten Steps of Universal Precautions in Pain Medicine

1. Diagnosis with appropriate differential
2. Psychological assessment, including the risk of substance use disorders (SUDs)
3. Informed consent
4. Treatment agreement
5. Pre/post intervention assessment of pain level and function
6. Initiate pain management intervention
7. Reassessment of pain score and level of function
8. Regularly assess the "four a's" of pain medicine: analgesia, activity, adverse reactions, and aberrant behavior
9. Periodic review of diagnosis and comorbid conditions, including SUDs
10. Documentation

Note: Step 6 of the original guideline was updated in line with the most recent CDC guidelines.

Screening for Risk of Mon-medical Opioid Use or Opioid Use Disorder

While the 2016 CDC guideline for prescribing opioids for chronic non-cancer chronic pain does not recommend initiation of LTOT, some people with chronic pain will likely be prescribed LTOT. Additionally, a large number of patients are currently receiving LTOT or are being actively tapered off LTOT. Thus screening for non-medical opioid use and OUD is important.[76]

Opioid Specific Screeners

The Screener and Opioid Assessment Tool for Patients with Pain, Revised (SOAPP-R),[77] Opioid Risk Tool (ORT),[78] Current Opioid Misuse Measure (COMM),[79] and Pain Medication Questionnaire (PMQ)[80] screen for non-medical opioid use behaviors. The DIRE (Diagnosis, Intractability, Risk, Efficacy) assesses the risks and benefits of continued LTOT.[81] A comparison of these screens suggests that all have some value and are most useful when supplemented by a clinical interview.[82]

Non-opioid Screeners

Common screening instruments for non-opioid substances include the alcohol use disorder identification test (AUDIT),[83] and Cannabis Use Disorder Identification Test-Revised (CUDIT-R),[84] the Drug Abuse Screening Test (DAST-10),[85,86] and the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[87] Finally, the simple four-item CAGE (Cut down, Annoyed, Guilty, Eye-opener) inventory was modified to screen for SUDs[88] (Box 52.2).

• BOX 52.2 CAGE* Questions Adapted to Include Drugs (CAGE-AID)

1. Have you felt you ought to cut down on your drinking or drug use?
2. Have people annoyed you by criticizing your drinking or drug use?
3. Have you felt bad or guilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?

**C*, Cut down; *A*, annoyed; *G*, guilty; *E*, eye opener.

The Opioid Crisis and Evolving Guidelines for the Use of Opioid Medications to Manage Pain

As prescriptions for opioid medication for non-cancer chronic pain escalated in the 1990s, there were substantial increases in the rates of OUD, admissions to addiction treatment facilities, and overdose deaths.[89] According to data from the Centers for Disease Control and Prevention (CDC), fatal poisonings involving opioids quadrupled between 2000 and 2014 from 1.5–5.9 deaths per 100,000.[90] Because of the opioid crisis, a major focus of opioid-related research in the last decade has centered on the prevention and treatment of non-medical opioid use and OUD. Non-medical opioid use includes behaviors such as taking a higher dose of an opioid medication than prescribed, using prescription opioid medications to manage symptoms other than pain, including depressed mood and using non-prescribed substances in addition to opioid analgesics (e.g. alcohol or cannabis). While patients with non-medical opioid use do not automatically meet the diagnostic criteria for OUD, repeated exposure to opioids places those on LTOT with non-medical opioid use at a higher risk of adverse events, including addiction and overdose. As noted previously, a systematic review estimated that among individuals with chronic pain who are prescribed opioids, rates of non-medical opioid use were estimated to be between 21% and 29%, and rates of OUD were between 8% and 12%.[36] Among those hospitalized for chronic pain between 2011 and 2015, the prevalence of OUD was approximately 7%, with an upward trend between 2011 and 2015.[91] In 1990, OUD was the 11th leading cause of disability-adjusted life years; by 2016, it became the seventh.[92] It is also important to note that the prevalence of non-medical opioid use is also relatively common among the general United States population. For example, in 2019, an estimated 10 million people aged 12 years and older had misused prescription opioids at least once in the past year.[35]

In response to the opioid crisis, in March 2016, the Centers for Disease Control and Prevention (CDC) released *the guideline for prescribing opioids for chronic pain*.[75] Although the CDC guidelines were met with some controversy,[93,94] subsequent studies continue to call into question the long term efficacy of LTOT and have found support for the risks associated with LTOT over time, especially at higher doses.[95–98] However, it is important to emphasize that for patients receiving LTOT for whom benefits outweigh harm, a continuation of LTOT along with close monitoring is reasonable. It is not evidence-based or concordant with CDC guidelines to taper involuntarily patients who are not experiencing harm from LTOT, and this practice may pose additional risks.[99] Bohnert et al. used a national data set of opioid prescriptions dispensed between 2012 and 2017 and identified decreases in rates of high dose and overall opioid prescribing following implementation of the CDC guidelines. In January 2012, the rate of high dose opioids (≥90 daily milligram morphine equivalents [MME]) was 683 per 100,000 persons, which decreased to 356 by December 2017. The overall opioid prescribing rate (per 100,000) decreased from 6577 opioid prescriptions dispenses (per 100,000 persons) in January 2012–4240 in December 2017.[98]

Medication for Opioid Use Disorder

Medication for opioid use disorder (MOUD), in combination with behavioral counseling, is the standard of care treatment for OUD.[3] MOUD reduces OUD related harm, including mortality and infectious disease transmission (e.g. HIV, hepatitis C, endocarditis).[4,100–102] MOUD consists of opioid agonist treatment

involving the long-acting full agonist methadone, partial agonist buprenorphine (most commonly prescribed in combination with the antagonist naloxone), or opioid antagonist naltrexone. Methadone is available from tightly regulated opioid treatment programs, which require six visits per week for supervised consumption for at least the first three months of treatment.[103,104] Buprenorphine may be prescribed by physicians and other practitioners depending on state regulations (e.g. advanced practice nurses and physicians associates) who have sought additional training (8 h for physicians, 24 h for advanced practice nurses and physicians associates) to obtain a waiver from the Drug Enforcement Administration (DEA) to treat OUD.[103] The government places patient limits on waivered providers: a 30 patient cap is in place the first year of waivered practice for most providers, with expansion to 100 patients in subsequent years. Providers with board certification in addiction medicine or psychiatry or who practice in certain settings can qualify for a 100 patient cap their first year, which expands to 275 the following year.[105] There are no specialty limits on who can seek additional training and a DEA (Drug Enforcement Administration) waiver. Thus obtaining a waiver might be useful for pain physicians interested in treating OUD in their own clinics.[105] Both methadone and buprenorphine are initiated at low, often sub-therapeutic doses, which are tapered over several weeks to find an individualized dose that reduces OUD symptoms without causing adverse effects (e.g. sedation).[103]

Iatrogenic Opioid Use Disorder

The indicators of iatrogenic OUD (i.e. OUD that occurs in the course of medically supervised opioid analgesic therapy) can be more subtle than those displayed for OUD related to recreational opioid use.[60] Loss of behavioral control, a key sign of addiction, may involve taking more opioids than prescribed, followed by visits to the emergency department or soliciting multiple prescribers for opioids; consequently, prescribers should check online state prescription drug monitoring programs to ascertain patients' use of controlled medications. Family members may also be useful in ascertaining possible indicators of iatrogenic OUD (e.g. patients lose the thread of conversation or fall asleep at inappropriate times).[60] Guidelines to date do not identify specific prescriber steps to take when concerns arise about medication-taking behaviors. However, a Delphi study of clinical experts suggests a patient-centered discussion of patients' behaviors, a recapitulation of the opioid treatment agreement, and providing a clear rationale for any decision to discontinue or taper opioid therapy.[106] However, it is important to note that some clinicians may encounter institutional or state policy pressure to discontinue opioids quickly.[106,107]

What to Do With Patients on Long-term Opioid Therapy With Suspected Opioid Use Disorder?

The development of OUD among patients prescribed opioids is a leading concern for both pain providers and patients.[108–110] Patient-centered tapering from LTOT may be appropriate in patients who feel their current opioid medication regimen is not effective or for whom risks outweigh the benefits.[111] For many patients who have been prescribed LTOT, switching to non-opioid therapy may not be feasible or in their best interest. One promising strategy in this scenario is to transition from LTOT to buprenorphine, which has a lower risk of adverse events, particularly for patients who have been on high opioid doses (>50 mg MME).[112–114] Although buprenorphine is classified as a partial mu agonist, it was initially developed to treat pain, and research has demonstrated that its risk profile may be safer than other opioids, and it may be effective for a wide range of pain types.[113–115] Additionally, there are options for patients who display signs or symptoms of OUD that still involve treating their pain. The standard of care treatment for OUD with MOUD is effective in reducing morbidity, mortality, and craving because of OUD.[4,102] For patients who are not currently enrolled in treatment for OUD, the following steps may help determine whether to continue LTOT or alter the treatment regimen[112]:

Step 1: Does the patient meet the criteria (see "Nomenclature") for a DSM-5 OUD? If so, go to Step 2. If not, go to step three.

Step 2: For patients meeting the criteria for OUD, urgent treatment using the standard of care, MOUD with methadone, buprenorphine, or naltrexone (see section "Medication for Opioid Use Disorder"). Opioid agonist therapy (methadone or buprenorphine) may be the preferred option among patients currently receiving LTOT because of the requirement of a seven to ten day washout period to prevent precipitated withdrawal with naltrexone.[103] Referral to an addiction specialist or opioid treatment program in this instance is warranted unless the pain management clinic has practitioners who have completed the DEA waiver process to prescribe buprenorphine.

Step 3: For patients not meeting the criteria for OUD, conduct a risk-benefit analysis for the continuation of LTOT. Factors that increase the risk of overdose or the development of OUD (i.e. medication interactions, age >65 years, reduced renal or hepatic function, and risk of respiratory depression).[116] The 2016 CDC guidelines consider improved pain and functioning as benefits that might lead to the continuation of LTOT.[75] For patients receiving doses below 50 mg MME of opioids and for whom the benefits of LTOT outweigh the harm, monitoring with routine reassessment may be appropriate. Switching to buprenorphine or approaching the topic of a patient-centered opioid taper is recommended for patients on daily doses greater than 50 mg MME or for those below 50 mg MME for whom benefits do not outweigh risks.[117]

Non-opioid Pharmacotherapy for Comorbid Pain and Substance Use Disorders

There is increasing evidence that the potential for harms of LTOT outweigh the benefit,[97,118] and non-opioid treatments are now the recommended first line treatment for anyone with chronic non-cancer pain.[75]

Non-opioid Pharmacotherapy

Depending on the type of pain being treated, medications to consider might include nonsteroidal anti-inflammatory drugs, anti-convulsant medications, and serotonin-norepinephrine reuptake inhibitors (SNRIs).[75] However, we note that newer data indicate that the anti-convulsant medications gabapentin and pregabalin have misuse potential, and they may increase the risk of respiratory depression and overdose among those currently using opioid medications.[119,120] Notably, some medications and non-pharmacologic therapies that treat pain have applications in the treatment of SUDs and vice versa.[112] Pain providers are sometimes surprised to learn that medications prescribed to treat chronic pain may also be indicated in the treatment of SUDs.[112] In the section below, we briefly describe pain and SUD use for common medications. We encourage pain clinicians to consult with their patients' addiction

providers to discuss dosing and applications of such medications, as the effective dose for SUD treatment might differ from the typical pain regimen. For patients with OUD, it is also worthwhile to consider altering a patient's pain regimen to incorporate medication that might treat their symptoms of both chronic pain and OUD, in collaboration with their addiction medicine provider. Notably, the use of adjunct medications that may cause sedation or increase the risk of respiratory depression (i.e. muscle relaxants, antiepileptics, benzodiazepines, and amitriptyline) is generally not recommended in patients currently receiving prescription opioids.[113]

Anti-convulsants

Pain physicians are likely to be familiar with the application of anti-convulsants, including gabapentin, pregabalin, and oxcarbazepine for neuropathic pain and fibromyalgia,[121,122] and topiramate for preventive migraine therapy. Topiramate has been investigated for neuropathic pain and fibromyalgia and found to have no benefit.[123,124] Research suggests that gabapentin may offer clinical benefits to patients with alcohol use disorders. Multiple studies have demonstrated reductions in cravings and alcohol use behavior among patients with AUD (alcohol use disorder) taking gabapentin compared to placebo, with some reporting improvements in mood and insomnia.[125–127] In December 2019, the FDA released a drug safety communication about the risk of respiratory depression with gabapentinoids combined with other central nervous system (CNS) depressants, particularly opioids, and how this impacts the future use of gabapentinoids in pain management is an evolving issue.[128] Topiramate has also shown clinical benefit in AUD, and some initial studies suggest that it could be applied in cocaine use disorder and tobacco use disorder, although much more research is needed.[129,130]

Muscle Relaxants

Baclofen has been used to treat spasticity and hypertonicity, particularly in conditions such as multiple sclerosis. Systematic reviews evaluating research into baclofen's utility in treating alcohol use disorder have not demonstrated a clear benefit, but this is an area of active investigation,[131,132] particularly among patients who are currently abstinent from alcohol.[133] Please see Chapter 55 for a more detailed description of the role of muscle relaxants in treating pain.

Benzodiazepines

Although the combination of benzodiazepines and opioids increases the risk of overdose, sedation, and OUD development, estimates for co-prescription are as high as 40% in outpatient settings.[134,135] Benzodiazepines are an important treatment for alcohol withdrawal syndrome that prevents seizures. However, outside of this indication, caution should be exercised when prescribing benzodiazepines in patients taking opioids.

α-2 Agonists

α-2 adrenergic receptor agonist drugs are commonly used for anesthesia.[136] For example, clonidine can provide prophylactic cardiovascular protection during intubation, while tizanidine can assist in the management of spasticity related to cerebral palsy. Although the α-2 agonist lofexidine is FDA-approved to manage symptoms during opioid withdrawal, clonidine is commonly used off-label for a similar indication. Studies have demonstrated the clear efficacy of these agents. However, they may have more side effects not seen with other agents such as methadone and buprenorphine and may not completely eliminate withdrawal syndrome-associated discomfort.[137]

Importance of Non-pharmacologic Pain Management Interventions

A recent systematic review focused on non-invasive non-pharmacologic treatment for chronic pain (without SUD) concluded that exercise, multi-disciplinary rehabilitation, acupuncture, cognitive behavior therapy (CBT), mindfulness practices, and mind-body practices most consistently exhibit modest improvements in pain intensity and function for specific pain conditions compared to usual care, sham treatments, or attention controls.[138] A narrative review that included 56 studies on psychosocial interventions for those with chronic pain and OUD underscored the promise that a similar group of psychosocial interventions including CBT, acceptance and commitment therapy, mindfulness-based cognitive therapy, mindfulness-based stress reduction, relapse prevention, and motivational enhancement therapy (MET).[139] Recognizing triggers (for pain and substance use), awareness of negative emotions, enhancing positive coping strategies, and pleasurable activity planning from both pain and SUD approaches are important elements of a hybrid psychosocial intervention that addresses both pain and SUDs.[140] A recent literature review focused specifically on treating those with pain and OUD described some evidence for stepped care approaches in primary care and emphasized the need for more integrated and multi-disciplinary services.[141]

Non-pharmacologic Interventions for Patients with Comorbid Pain and SUDs

A growing body of literature has examined the efficacy and effectiveness of behavioral interventions among patients with concomitant SUD and chronic pain. Some trials included those with a heterogeneous group of SUDs, while others focused on specific SUDs. Among those with more heterogeneous SUDs, the eight week improving pain during addiction treatment behavioral pain management intervention, which focused on relapse prevention and pain management skills, was associated with higher pain tolerance in men and lower pain intensity in women compared to those randomized to a supportive psychoeducational control. However, there were no differences in substance-related outcomes.[142] Other trials included those with specific SUDs. One recent study examined a mindfulness-oriented recovery enhancement intervention in patients with OUD and chronic pain and found that the eight week intervention improved opioid craving, pain unpleasantness, and increased positive affect compared to treatment as usual.[143] Pilot studies have demonstrated the feasibility and efficacy of CBT combined with MOUD for patients with comorbid pain and OUD with both methadone[144] and buprenorphine.[145] In a 12 week pilot study among 40 patients with OUD and low back pain receiving MMT (methadone maintenance treatment), patients reported higher satisfaction with CBT compared to methadone drug counseling as usual, and the CBT group contained a higher proportion of patients with negative urine drug screens for illicit opioids, with similar results for pain interference in both groups.[144] Another study demonstrated repeat attendance and high satisfaction in patients receiving MMT who attended CBT-informed counseling groups for pain.[146] Finally, a study of a brief smoking cessation intervention among those with chronic pain found that those randomized to the intervention had increased willingness to consider cessation.[145]

Managing Acute Pain in Patients With Chronic Pain and Opioid Use Disorder

Management of acute pain in patients receiving opioids, such as LTOT or MOUD, or with SUD histories, can be challenging. Patients who receive opioids may require increased doses of opioids to achieve pain relief because of increased tolerance to opioids and opioid-induced hyperalgesia.[147,150] Physicians may be wary of prescribing opioids to patients with a history of SUD, depriving these patients of pain relief following trauma, surgery, or other procedures resulting in acute pain. Patients with SUDs may also be hesitant to receive opioids out of fear they might relapse or develop OUD. Concern about inappropriate opioid prescribing and how to manage the large population of patients hospitalized for acute or chronic pain has led professional societies to develop guidelines for post-procedure analgesia in all patients. While these guidelines are not targeted specifically for populations with SUDs or chronic pain, they are useful for clinical practice or when helping a patient prepare for a procedure or intervention.[151–153] Strategies such as comprehensive pain plans for both individuals and institutions that include explicit guidance for emergency and hospital providers on how to manage an individual patient's acute pain flares may also be helpful for certain conditions. For example, the implementation of individualized protocols for acute pain in sickle cell disease has been shown to reduce admissions and readmissions, improve patients' pain, and provide patient satisfaction,[154] and is recommended by expert guidelines.[155]

More research is needed on the optimal management of acute pain in patients receiving MOUD, but there is evidence that continuing MOUD during surgery or treatment for acute pain is important.[149,156] The ASAM guidelines released in 2020 suggest that it may be appropriate to temporarily increase daily doses of opioid agonists or split doses to optimize pain management in patients receiving MMT and buprenorphine during acute pain episodes.[149] Guidelines from ASAM and the Pain and Addiction Interdisciplinary Network support the use of high dose opioid agonists for refractory pain in patients receiving buprenorphine for OUD,[157] and ASAM recommends this for patients receiving MMT as well. For patients receiving naltrexone, options during acute pain include local pain management (i.e. nerve blocks), use of sedatives including ketamine and benzodiazepines, non-opioid pharmacology, or overcoming the blockade of mu receptors with high potency opioids. In preparation for surgery, patients can discontinue naltrexone at a minimum of 72 h prior and require three to seven days without opioids before resuming naltrexone to avoid precipitated withdrawal.[149] For patients who make the decision with their care team to stop methadone or buprenorphine before surgery, ASAM now recommends discontinuation only the day prior to or day of surgery and that prescribers should determine how to resume.[149]

Cannabis Use for Pain and Cannabis Use Disorder

The availability and use of cannabis for chronic pain is increasing despite mixed evidence for its effectiveness and potential for harm,[158] including addiction (see also Chapter 56). Among regular users, cannabis use can lead to physiologic dependence with a withdrawal syndrome that may include dysphoric mood, disturbed sleep, gastrointestinal symptoms, and decreased appetite. Among adults, the overall prevalence of CUD is 2.5% over 12 months and 6.3% over a lifetime.[50,23] Furthermore, among those reporting past year cannabis use, 36% met the criteria for CUD over the previous year.[159] While CUD is more prevalent and of greater severity than many recognize, only 5% of those with CUD have sought treatment from a healthcare provider.[50]

Standard treatment of CUD includes psychotherapy, such as CBT, MET, or contingency management (CM).[160] However, these treatments may be inaccessible as well as time-and resource-intensive. Currently, no FDA-approved pharmacotherapies are available for CUD, although a number (e.g. cannabinoids, antidepressants, anxiolytics, and glutamatergic modulators) have been proposed for off-label use.[161] A recent systematic review on the treatment of CUD concluded that there is a dearth of evidence examining pharmacologic interventions for CUD, although there is evidence that several drug classes, including cannabinoids and selective SNRIs, are ineffective.[162]

Clinical considerations for those treating chronic pain among individuals with cannabis use include awareness of state, federal, and institutional policies regarding cannabis, the establishment of goals regarding cannabis use, screening for non-medical use and addiction, counseling patients on harms and risks, offering medical advice on routes of administration, continual monitoring of functional status, symptom severity, and use of other medications and substances; use of urine drug tests; monitoring for harms associated with cannabis (falls, cognitive issues, motor vehicle accidents), and providing advice on discontinuation or referral to SUD treatment.[49]

Importance of Coordinated Care

Many providers who treat chronic pain may be wary of the clinical complexity of accepting a new patient who is currently receiving treatment for OUD. We encourage pain providers to connect with the patient's MOUD program and prescriber. While research shows that providers treating chronic pain feel like they are less experienced in treating SUDs, addiction treatment providers reveal similar concerns about their experience and training surrounding pain treatment.[163,164] Pain providers have a lot to offer their colleagues in addiction medicine in terms of knowledge and experience of managing pain. Coordination between the two specialties can result in a better experience for the patient and the providers.

Conclusion

Chronic pain and SUDs are prevalent chronic medical conditions that often co-occur. Patients with both conditions are clinically complex and may have other comorbid psychiatric and medical conditions. While many patients have received long term opioid therapy for chronic pain over the last three decades, expert guidelines now recommend against LTOT for most patients, given the risk of opioid-related harm. There are high rates of chronic pain in patients with SUDs. Likewise, many patients with chronic pain have SUDs and may use substances to manage their pain. The clinical needs of patients can go untreated because of fragmented care for pain and SUDs. While there are effective treatments for SUDs, particularly MOUD for those with OUD, many patients with SUDs do not receive evidence-based treatment. There are also promising non-opioid interventions for chronic pain and SUDs, including non-opioid pharmacotherapy and non-pharmacologic pain management interventions. Pain treatment providers should screen for SUDs. If they are unwilling or unable to provide both SUD and pain management, they should consider coordinating care with addiction medicine providers. In the case of OUD, buprenorphine prescribing by licensed office-based clinicians provides an increased opportunity for pain providers to be part of the treatment for co-occurring chronic pain and OUD.

Key Points

- Addiction is a chronic relapsing medical condition or disease with effective treatments, similar to diabetes or hypertension.
- There are high rates of SUDs among patients with chronic pain and high rates of chronic pain among patients with SUDs.
- Pain clinicians should screen for addiction risk before and during treatments, especially for treatments involving controlled substances, and be prepared to either provide treatment for SUDs or offer treatment referrals.

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53
Anti-depressants

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Introduction

The second half of the 20th century saw the introduction of a range of therapeutic agents known to have an anti-depressant effect. These are currently classified partly based on their chemical structure and partly according to their primary *in vivo* effects (Box 53.1). Even before their introduction into clinical practice, the concept of an association between depression and pain was clear, and the possibility that this link was causal encouraged the use of anti-depressants for patients who exhibited features of both pain and depression. It is now recognized that the pain relief apparent with the use of anti-depressants can be independent of any alteration in mood caused by the drug,[1] and the analgesic effects can occur more rapidly,[2,3] at lower doses/serum levels than those required for anti-depressive effects.[4,5]

Our current understanding is that the primary mechanism of action of anti-depressant drugs in neuropathic pain is through blocking monoamine reuptake in descending modulatory pathways. In a normal state, activity within bulbospinal circuits are finely balanced to set the sensory gain at the spinal level, and these can rapidly adapt to amplify or suppress pain according to context. For example, neural circuits have been described that underly acute stress-induced analgesia and chronic stress-induced hyperalgesia,[6] and placebo responses are also in part because of recruitment of descending opioidergic inhibitions.[7]

Serotonin (5-HT) originating from the dorsal raphe nuclei exerts bi-directional control of sensory neuronal activity at the spinal level dependent on the particular receptor subtype targeted. At the cellular level, 5-HT receptors can be excitatory (subtypes 2, 3, 4, 6, and 7) or inhibitory (subtypes 1, 5). However, the complexity of their ability to amplify or suppress sensory transmission is determined by their expression patterns on excitatory and inhibitory interneurons.[8] The 5-HT_{2A} and 5-HT_{3} receptors are the predominant faciliatory receptors in the dorsal horn, and their excitatory effects on pre-synaptic primary afferent terminals outweigh their actions on inhibitory interneurons.[9,10] The 5-HT_{7} receptor conversely has a greater expression on inhibitory interneurons, and agonists suppress sensory transmission.[11] Running parallel to these serotonergic projections to the dorsal horn are pontine derived noradrenergic pathways, particularly from the A5 and A6 (locus coeruleus) groups; these terminate upon spinal α_1 and α_2 adrenoceptors. Activation of the α_2 adrenoceptor inhibits neuronal excitability, and these are largely expressed pre-synaptically on primary afferent terminals (α_{2A}) and excitatory interneurons (α_{2C}). Conversely, α_1 adrenoceptors are excitatory and are expressed by both inhibitory and excitatory interneurons. However, their net effect on sensory transmission is considered to be faciliatory.[8] There is compelling evidence that links a loss of noradrenergic inhibitory tone and enhanced serotonergic facilitation in the development and maintenance of chronic pain states.[12–15] Consequently, this imbalance in descending monoaminergic control in neuropathic rats can also present as a loss of diffuse noxious inhibitory controls (DNIC).[16] DNIC are a partly opioidergic and noradrenergic endogenous pain modulatory mechanism.[16,17] In the absence of nerve injury, DNIC are activated when two distant noxious stimuli are applied, recruiting a bulbospinal inhibitory pathway that overlaps with the canonical descending pain modulatory network.[18]

The human counterpart measure to DNIC is referred to as conditioned pain modulation (CPM; see Chapter 21). Typically, CPM is performed by determining pain scores (on a visual analog scale) or a pain threshold to a noxious test stimulus, followed by a repeat of the test in the presence of a distant heterotopically applied noxious conditioning stimulus, e.g. cold pressor. Functional CPM is then quantified as the decrease in pain scores or increase in pain threshold to the test stimulus. The use of CPM as a sensory testing tool has gained much traction in recent years to study the role of descending modulation in the cause of pain. Low CPM is associated with numerous chronic pain states of neuropathic and non-neuropathic origin,[19–23] and a higher risk of postoperative pain.[24,25] As an illustration of how patients can be separated according to putative pathophysiologic mechanisms, a large scale study attempting to stratify chronic pain patients according to mechanisms of spinal gain (enhanced temporal summation) or loss of descending control (low CPM) reported 37% of patients with low CPM and 21% with both low CPM and enhanced temporal summation.[26] Stratification will be key to future clinical trial design and treatment selection, given that nerve injury can induce numerous transcriptional changes and neuroplasticity throughout the sensory neuraxis. Any given drug with a defined mechanism of action would have to target the predominant pathophysiologic mechanism in a patient to provide relief. In this respect, it is perhaps unsurprising that many patients fail to achieve adequate pain relief.

The focus of this chapter is on the potential pain-reducing capability of drugs otherwise associated with the treatment of depression. In most cases, the clinical studies cited within are based on non-stratified patient cohorts and commonly use patient reported ongoing pain scores as primary endpoints of efficacy. However,

• BOX 53.1 Classification of Anti-depressants

Tricyclic Anti-depressants

Amitriptyline
Clomipramine
Desipramine
Dothiepin
Doxepin
Imipramine
Iprindole
Lofepramine
Nortriptyline
Opipramol
Protriptyline
Trimipramine

Serotonin-Noradrenaline Reuptake Inhibitors

Duloxetine
Milnacipran
Nefazodone
Venlafaxine

Selective Serotonin Reuptake Inhibitors

Alaproclate
Citalopram
Escitalopram
Etoperidone
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Zimeldine

Monoamine Oxidase Inhibitors

Harmaline
Iproclozide
Iproniazid
Isocarboxazid
Moclobemide
Nialamide
Selegiline
Toloxatone
Tranylcypromine

Dopamine Reuptake Inhibitors

Amineptine
Bupropion

Noradrenaline Reuptake Inhibitor

Reboxetine

Selective Serotonin Reuptake Enhancer

Tianeptine

Tetracyclic Anti-depressants

Amoxapine
Maprotiline
Mianserin
Mirtazapine

more recently, trans-etiological sensory phenotypes have been described, and each may have specific drug sensitivities determined by common underlying mechanisms (see Chapter 21).[27] The prospects for mechanism-led treatment selection regarding anti-depressants will also be addressed.

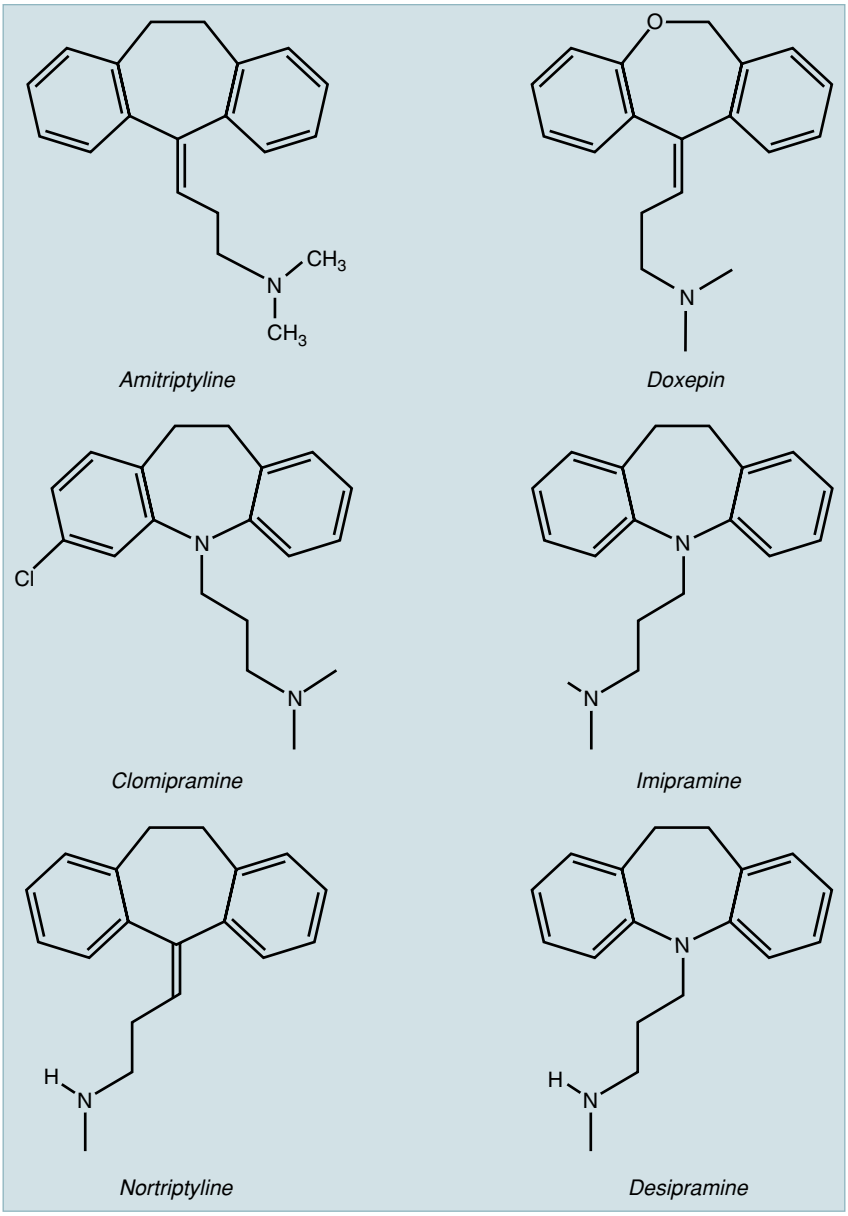
Tricyclic Anti-depressants

Mechanism of Action (Animal Models)

In addition to increasing synaptic monoamine concentrations, tricyclic anti-depressants (TCAs; Fig. 53.1) exert many pharmacologic actions. Table 53.1 compares the receptor affinity profiles for various TCAs. All TCAs have a low affinity for dopamine transporters but different binding profiles for serotonin and noradrenaline transporters. Amitriptyline has a comparable affinity for both transporters, whereas desipramine has higher selectivity for noradrenaline transporters (approximately 40-fold) and clomipramine has higher selectivity for serotonin transporters (approximately 230-fold). Despite having a low affinity for dopamine reuptake transporters, systemic amitriptyline promotes dopamine release at the spinal level in neuropathic rats, and antinociception is partially blocked by a D_2 receptor antagonist.[28] A possible explanation is an interaction between monoamine systems at the spinal level. Plasticity in the expression of serotonergic or noradrenergic receptors on dopaminergic terminals could promote the release of dopamine. Alternatively, this interaction may occur in higher centers leading to a top-down increase in descending dopaminergic drive. A potential confound is the role of dopamine in motor function and motivation that could alter behavioral responses to painful stimuli.

Dual blockers of serotonin and noradrenaline reuptake, such as most TCAs and serotonin-noradrenaline reuptake inhibitors (SNRIs), are known to be more effective for pain relief than the transporter selective drugs. As there is a considerable anatomic and functional interaction between the signaling systems, drug actions on one system will inevitably impact the other, which likely produces synergistic drug effects.[29] Modulation of coerulospinal activity is central to the anti-nociceptive effects mediated by TCAs and SNRIs. At the spinal level, amitriptyline increases spinal noradrenaline concentrations in neuropathic rats, coinciding with a reversal of evoked hypersensitivity and restoration of DNIC.[30] Increased release of noradrenaline within the locus coeruleus can exert excitatory or inhibitory effects on neuronal activity via α_1 and α_2 adrenoceptors, respectively. However, long-term desipramine and duloxetine dosing leads to the desensitization of α_2 autoreceptors and may restore descending inhibition.[31] Plasticity in channel function within the dorsal horn, such as increased receptor density and enhanced coupling to G-proteins, could also increase the magnitude of drug effects in pathophysiologic states.[32,33]

TCAs may mediate part of their analgesic effects via activation of opioidergic signaling.[34–36] The anti-nociceptive effects of chronic nortriptyline dosing were reversed by naloxone and selective antagonists of δ- and κ-Opioid receptors,[34] but not μ-Opioid receptors.[35] TCAs tend to have a low affinity for opioid receptors. Therefore these effects are considered secondary to other mechanisms such as changes in monoamines. Concerning other central targets, TCAs might also act to reverse central sensitization by targeting NMDA receptors, either directly[37] or through downregulation of NR2B subunits.[38] More recent investigations have revealed novel insight into potential peripheral mechanisms of analgesia. TCAs have been proposed indirectly to modulate neuroimmune responses such as downregulation of tumor necrosis factor (TNF) α and the nuclear factor κB (NFκB) signaling pathway, which reduces inflammatory sensitization of peripheral sensory neurons.[39–41] *In vitro* studies have shown that various TCAs are activation state- and use-dependent blockers of $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$ with IC50s in the range of therapeutic plasma concentrations for the treatment of depression and neuropathic pain.[42,43] The latter channels $Na_v1.7$ and $Na_v1.8$ are almost exclusively expressed in nociceptors,[44,45] whereas $Na_v1.3$ is not normally expressed in adult neurons but is upregulated after nerve injury and promotes hyperexcitability.[46] There are some suggestions that amitriptyline can also reduce peripheral neuronal hyperexcitability by inhibiting adenosine reuptake.[47,48] However, there is no evidence that adenosine receptor agonists are effective against pain in clinical trials.[49] In all of these cases, it is impossible to ascertain that the non-monoamine actions contribute to pain control at clinical doses.



• **Figure 53.1** Tricyclic anti-depressants.

Clinical Management of Pain

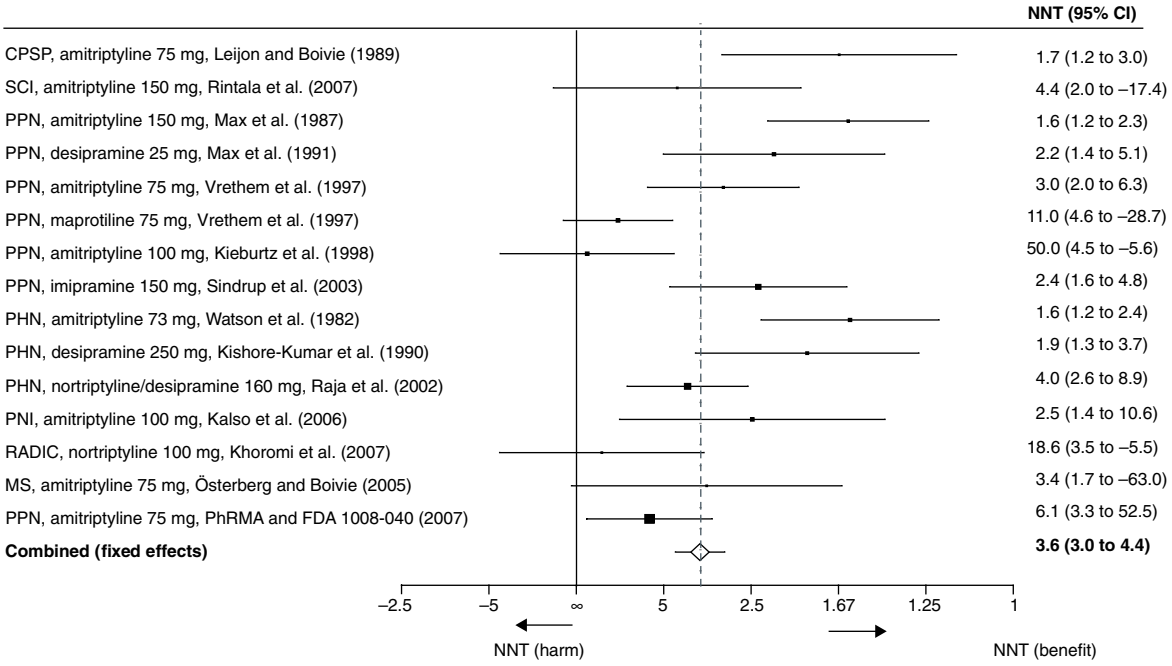
Drug efficacy is often evaluated in terms of the number needed to treat (NNT). In terms of analgesics, this represents the number of patients who need to take the treatment to obtain a 50% or greater reduction in their pain. A meta-analysis of double-blind placebo-controlled trials of TCAs in neuropathic pain calculates the NNT at 3.6 (Fig. 53.2),[50] a higher efficacy than most other treatments. TCAs appear effective in peripheral and central origin neuropathies, including diabetic neuropathy,[1,51–53] postherpetic neuralgia,[54–56] peripheral nerve injury,[57] spinal cord injury,[58] central post-stroke pain,[59] and multiple sclerosis.[60] Limited effectiveness was observed in a trial involving HIV neuropathy patients,[61] and radiculopathy.[62] Amitriptyline is the most widely studied,[1,53,56–61] but the NNT for desipramine,[51,54,55] nortriptyline,[55] and imipramine[52] appear comparable albeit based on a smaller dataset. As TCAs can block serotonin and noradrenaline reuptake, it seems likely that inefficient CPM could predict analgesic efficacy as has been demonstrated for duloxetine.[23] Local or topical delivery of drugs has been explored as a method to reduce central side effects of analgesics, and the TCAs were considered a potential candidate because of numerous off-target effects at various ion channels known to be expressed in primary afferents. However, no randomized, double-blinded, placebo-controlled trials support the efficacy of topical amitriptyline.[63] In patients unresponsive to oral TCAs, a small decrease in ongoing pain scores was observed with topical doxepin, but paresthesia, allodynia, and shooting pains were unaffected.[64]

Fibromyalgia is not classified as a neuropathic condition but shares features of neuropathic pain, such as central sensitization and altered central modulation. Dysregulation of descending modulation is apparent in some patients with fibromyalgia,[65] and pain facilitation as well as a loss of pain inhibition during CPM has been reported.[66] A meta-analysis of TCA trials in fibromyalgia indicates an overall small to moderate improvement of pain, sleep

TABLE 53.1 Affinity Profiles of TCAs for Various Transporters and Receptors

	SERT	NET	DAT	5-HT$_{1A}$	5-HT$_{2A}$	α_1	α_2	D$_1$	D$_2$	H$_1$	H$_2$	mACh
Amitriptyline	40	68	4000	450	21	15	581	89	885	1	66	16
Clomipramine	0.2	46	2600	>10,000	35	20	1862	219	143	22	209	37
Desipramine	112	2.9	>3000	>6400	350	49	2750	5462	2530	87	1549	205
Dothiepin	8.6	46	5310	ND	ND	ND	ND	ND	ND	ND	ND	64
Doxepin	68	30	>10,000	276	27	24	1185	ND	1380	0.27	ND	72
Imipramine	8.3	83	>8500	>5800	150	51	3150	>10,000	1115	9.3	550	62
Lofepramine	70	5.4	>10,000	4600	200	100	2700	ND	2000	245	4266	265
Nortriptyline	18	4	1130	294	ND	55	2000	ND	2570	3	645	37
Protriptyline	19.6	1.4	2100	ND	ND	130	6600	ND	2300	16.1	398	25
Trimipramine	149	2450	3780	ND	ND	24	680	ND	180	1	41	58

Values are K_i (nM) for human proteins, the smaller the K_i the greater the binding affinity. TCAs are inhibitors of transporters and antagonists/inverse agonists of receptors. Data from the Psychoactive Drug Screening Program K_i database, Roth and Driscol, University of North Carolina. (*SERT* - serotonin reuptake transporter, *NET* - noradrenaline reuptake transporter, *DAT* - dopamine reuptake transporter, *ND* - not determined).



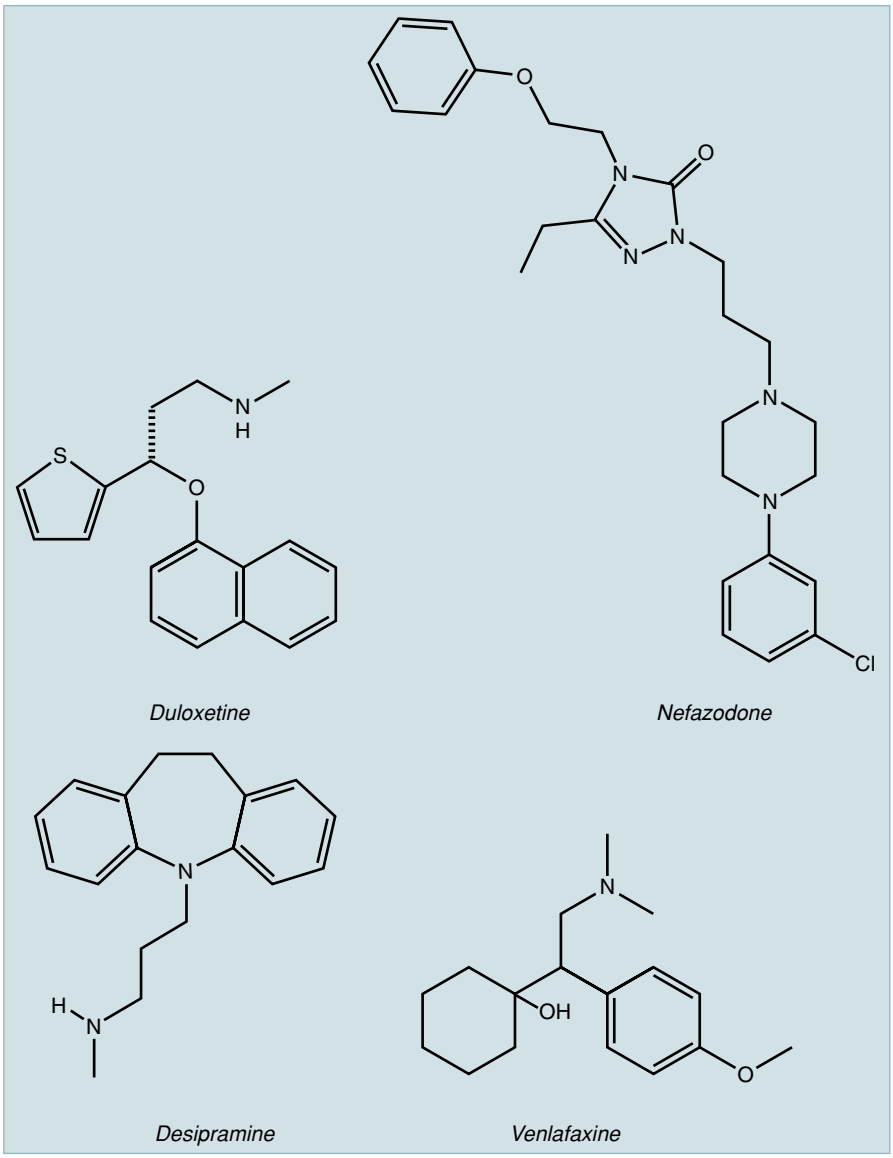
• **Figure 53.2** NNT values (with 95% confidence intervals) are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for tricyclic anti-depressants (15 studies, 948 participants). The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. *CPSP*, Central post-stroke pain; *FDA*, United States Food and Drug Administration; *MS*, multiple sclerosis; *NNT*, number needed to treat; *PHN*, postherpetic neuralgia; *PhRMA*, Pharmaceutical Research and Manufacturers of America; *PNI*, peripheral nerve injury; *PPN*, painful polyneuropathy; *RADIC*, painful radiculopathy; *SCI*, spinal cord injury pain. Data from Finnerup et al., Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–73.[50]

disturbances, and fatigue.[67] A small number of patients benefited greatly from treatment with anti-depressants. However, a large number are also known to drop out of trials because of intolerable adverse effects. It was suggested that TCAs appear more effective for patients with comorbid insomnia, whereas SNRIs may be preferable for patients with comorbid depression. Based on a lower meaningful effect size (reduction of pain by 30%), the NNT for TCAs in fibromyalgia is 4.9.

SNRIs

Mechanism of Action (Animal Models)

SNRIs (Fig. 53.3) selectively block the reuptake of serotonin and noradrenaline. Milnacipran has an equal affinity for serotonin and noradrenaline transporters, whereas duloxetine and venlafaxine have 10-fold and 30-fold selectivity for serotonin transporters,

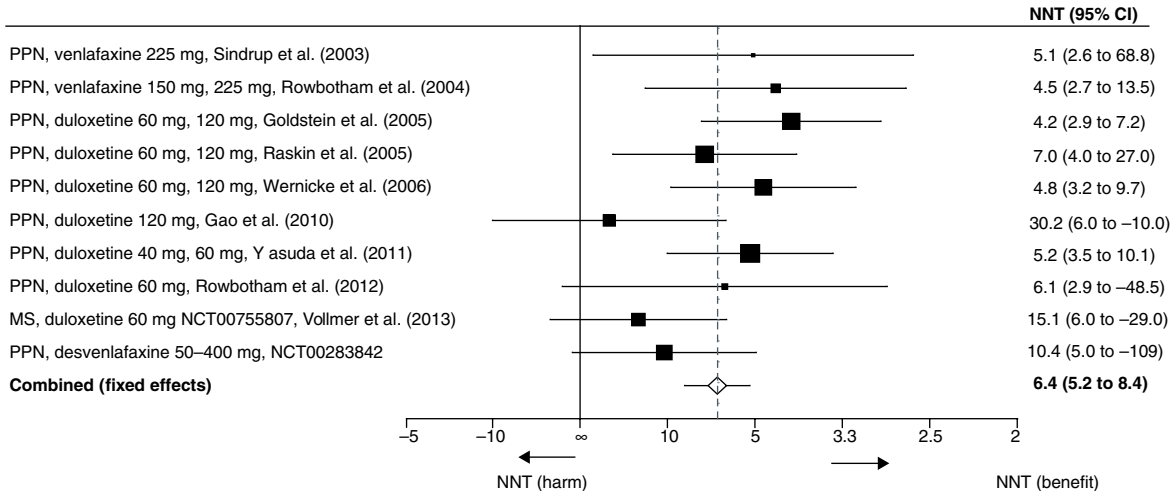


• **Figure 53.3** Serotonin-noradrenaline reuptake inhibitors.

respectively. A single systemic dose of duloxetine and milnacipran increases spinal concentrations of serotonin and noradrenaline though interestingly, the temporal kinetics of transmitter accumulation differ. Milnacipran increases both transmitter levels gradually with time. In contrast, duloxetine rapidly increases serotonin concentrations that decline with time, whereas noradrenaline concentrations increase progressively.[68] As discussed above, augmentation of noradrenergic signaling in the coerulo-spinal pathway is critical to the analgesic effects mediated by SNRIs. In neuropathic rats, duloxetine increases spinal noradrenaline content, and the anti-nociceptive effects are reversed by an intrathecal α_2 adrenoceptor antagonist.[69] In line with clinical observations,[23] DNIC are absent after nerve injury and are also restored by duloxetine.[69] There are conflicting data regarding the involvement of opioid signaling systems in the anti-nociceptive effects of SNRIs, and these effects differ according to the injury model and dosing protocols.[36,40,70,71] As this is a feature shared with TCAs, it seems likely that activation of endogenous opioid signaling occurs secondary to blocking the reuptake of noradrenaline and serotonin, which in turn could activate their respective receptors on inhibitory opioidergic interneurons in the dorsal horn. Peripheral actions of chronic duloxetine dosing have also been described, which rely on noradrenaline release from peripheral sympathetic terminals. This subsequently downregulates TNFα and NFκB pathways mediated via β_2 adrenoceptors on non-neuronal satellite cells in the dorsal root ganglia of neuropathic mice.[39,40]

Clinical Management of Pain

At present, duloxetine is the only licensed anti-depressant (in the United States) for the treatment of diabetic neuropathy, and approvals for fibromyalgia and chronic musculoskeletal pain have now been granted. A meta-analysis of double-blind placebo-controlled trials of SNRIs in neuropathic pain calculates the NNT at 6.4 (Fig. 53.4).[50] Against the primary endpoint of average pain scores, most trials in diabetic neuropathy patients reported decreased pain with duloxetine treatment (60-120 mg) compared to a placebo,[2,72–75] whereas one reported transient effects.[76]



• **Figure 53.4** NNT values (with 95% confidence intervals) are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for serotonin-noradrenaline reuptake inhibitors (10 studies, 2541 participants). The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. *CI*, Confidence interval; *MS*, multiple sclerosis; *NNT*, number needed to treat; *PPN*, painful polyneuropathy. Data from Finnerup et al., Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–73.

In addition, duloxetine improved several secondary quality of life endpoints across these studies, including sleep,[72,75] mood,[2,72] and mobility.[72,75,76] In a study involving multiple sclerosis patients, duloxetine was more effective than placebo treatment, but notably, the NNT appears considerably higher than for diabetic neuropathy.[77] The NNT for venlafaxine, and its active metabolite desvenlafaxine, is comparable to duloxetine.[52,78,79] However, the dosage might require consideration as venlafaxine is proposed to act primarily as a selective serotonin reuptake inhibitors (SSRI) at a dose of 75 mg and as an SNRI at doses above 150 mg.[80] Quantitative sensory tests indicate that venlafaxine inhibits evoked pains, including brush allodynia, pinprick hyperalgesia, and temporal summation in addition to ongoing pain.[81]

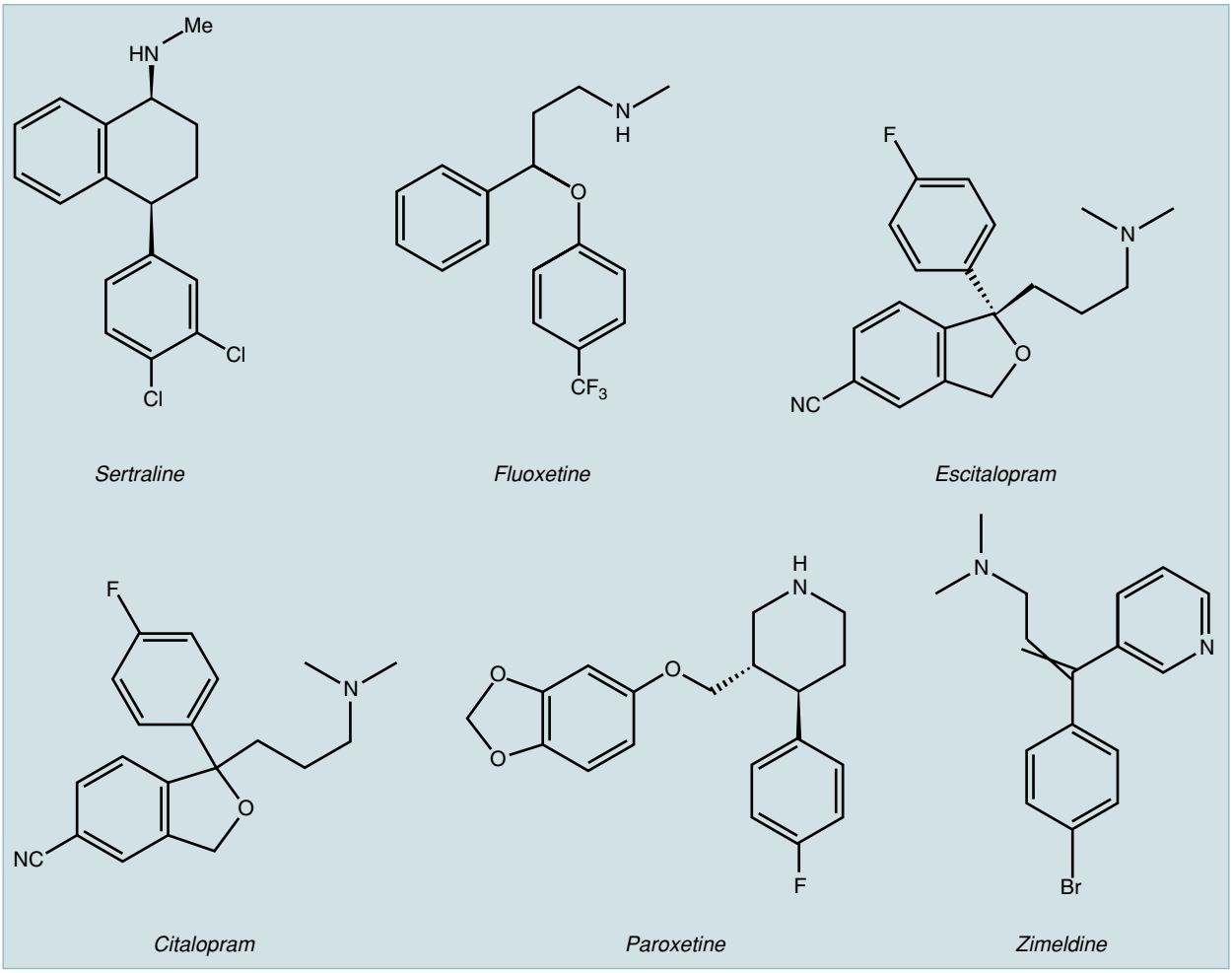
The high NNT values associated with anti-depressants, and other analgesics, have refocused trial design toward personalized approaches and predictive medicine. At present, there are no established sensory testing-led treatment algorithms, but in recent years there have been a few notable advances. Patients stratified according to hyperexcitable peripheral nociceptor function were more likely to benefit from the sodium channel blocker oxcarbazepine than those with a sensory loss phenotype.[82] *Post hoc* analysis of an overall negative pregabalin trial in HIV neuropathy revealed pain relief in patients with severe pinprick hyperalgesia.[83] Several have examined, with varying degrees of success, whether sensory phenotypes act as predictors of SNRI response.[84–86] One of the more elegant examples to date demonstrated that CPM efficiency in diabetic neuropathy patients correlated with analgesic outcomes.[23] The authors hypothesized that drugs should be prescribed according to the patient's pattern of pain modulation, and drugs that augment descending inhibition would benefit those that exhibited low endogenous pain modulation. Duloxetine (30-60 mg) efficacy was greater in patients with less efficient pretreatment CPM levels, whereas those with efficient CPM achieved little relief.[23] Similar outcomes have been observed with tapentadol (a dual μ-Opioid agonist/noradrenaline reuptake inhibitor [NRI]),[21] the common denominator with duloxetine being the NRI component. A caveat to interpreting CPM is that efficient CPM is considered the net inhibitory function extracted from the gross descending output. Hence an absence of CPM could result from enhanced facilitation, a loss of inhibition, or a combination of both. In a back-translational rodent study descending inhibition after nerve injury was vastly diminished and reversed by blocking spinal noradrenaline reuptake, but enhanced spinal 5-HT_3 mediated facilitations can mask residual inhibitory function, and DNIC was restored by a 5-HT_3 antagonist alone.[16] Thus an absence of effective CPM/DNIC could predict analgesia by agents capable of enhancing inhibitory signaling and/or reducing facilitatory activity.

SSRI

Mechanism of Action (Animal Models)

It was hoped that with the advent of anti-depressants with more specific modes of action, analgesia would still be associated with their use, and the potential to produce side effects would be reduced. However, studies in rodent models of neuropathy have produced mixed data on the efficacy of SSRIs (Fig. 53.5). Citalopram and fluoxetine do not appear to affect mechanical hypersensitivity after nerve injury.[34,87,88] However, citalopram partially reverses heat hypersensitivity.[87] At an effective dose, the SSRI fluoxetine attenuates nocifensive behaviors in short-term models of central sensitization, an effect that is diminished by depletion of endogenous serotonin.[89] However, at higher doses of SSRIs, analgesic effects could be attributed to non-selective actions at the noradrenaline transporter as paroxetine can increase spinal noradrenaline release.[90] In contrast, only spinal delivery of citalopram and fluoxetine restored deficient DNIC in neuropathic rats, whereas systemic doses were without effect suggestive of concomitant inhibitory/faciliatory actions at multiple sites. The effects of spinally delivered SSRIs were mediated via 5-HT_7 receptors allowing DNIC to be restored via α_2 adrenoceptors.[91]

Acute and chronic mechanisms of drug action in supraspinal structures can have complex actions on neuronal activity. Noradrenergic neurons in the locus coeruleus receive dense serotonergic projections, which exert tonic inhibitory influences on neuronal activity,[92] and this is augmented by SSRIs.[93] It is possible in a neuropathic state that the inhibitory spinal actions of SSRIs are countered



• **Figure 53.5** Selective serotonin reuptake inhibitors.

by further top-down suppression of descending noradrenergic inhibition. Within the dorsal raphe, spontaneous activity of putative serotonergic neurons is inhibited by SSRIs in a 5-HT_{1A} receptor dependent manner, but chronic dosing results in desensitization of 5-HT_{1A} auto-receptors leading to a recovery of activity.[94] In addition, cortico-limbic circuits are critical in assigning an emotional valence to sensory inputs, and these pathways are also subjected to serotonergic modulation. In a model of arthritis, inhibiting 5-HT_{2C} receptors within the basolateral amygdala potentiated the analgesic effect of fluvoxamine on supraspinal-organized behaviors (vocalizations and anxiety-like behaviors) but not spinal reflexes to painful stimuli.[95] The majority of rodent studies examine the acute effects of drugs. However, transcriptional changes can occur with chronic dosing, including altered expression of 5-HT_{2C} receptors at spinal and supraspinal sites,[96] and HDAC2 and mGlu2 receptors in the dorsal root ganglia, and dorsal horn, respectively.[97]

Clinical Management of Pain

Data from clinical trials provide weak evidence for the efficacy of SSRIs in the treatment of neuropathic pain. The lack of suitable comparable studies means that a reliable NNT has been difficult to calculate,[50] but is thought to be at least 6.7 for SSRIs, which is likely to be underestimated.[98] Three crossover studies in diabetic neuropathy patients compared the effects of citalopram, fluoxetine, and paroxetine (all 40 mg doses) to a placebo. Fluoxetine was found to be no better than placebo treatment,[4] whereas citalopram produced marginal improvement of pain.[99] Paroxetine reduced ongoing pain scores and paresthesia but provided no improvement in sleep disturbances and was considered less effective than imipramine.[100] Results from studies in fibromyalgia mirror the studies in neuropathic pain and are mixed at best. After a course of treatment with citalopram (20–40 mg), no improvements in pain scores, tender points, or depression scores were found,[101] and a separate study broadly reported similar findings with weak beneficial effects.[102] Trials of fluoxetine have reported similar outcomes with limited to no improvement of pain scores and tender points and inconsistent improvements in secondary measures such as sleep disturbances, wellbeing scores, and depression scores.[103–105]

Noradrenaline Reuptake Inhibitors

Mechanism of Action (Animal Models)

Reboxetine is a selective NRI with little or no affinity for serotonin and dopamine reuptake transporters. In a rodent nerve injury model, intrathecal reboxetine reverses the functional deficit in descending noradrenergic control by inhibiting evoked hypersensitivity and ongoing pain (conditioned place preference paradigm).[106] Similar actions are observed on evoked neuronal activity within the spinothalamic pathway in a pathophysiologic state dependent manner.[107] Furthermore, functional DNIC are blocked by an intrathecal α_2 adrenoceptor

antagonist, and intrathecal reboxetine restores absent DNIC in neuropathic rats.[16] This underlying noradrenergic mechanism explains the relationship between low CPM and the use of tapentadol (dual μ-Opioid agonist/NRI) and duloxetine (SNRI) for treating neuropathic pain.[21,23] Pontine derived noradrenaline projects throughout the neuraxis and has roles in regulating arousal, mood, learning, and memory. This functional dichotomy between the ascending and descending noradrenergic components may underly the negative side effects of systemic targeting of the noradrenergic system.[108]

Clinical Management of Pain

No comprehensive data has indicated that NRIs are suitable for treating neuropathic pain. Two Pfizer-led trials for postherpetic neuralgia and diabetic neuropathy were terminated because of a lack of efficacy (NCT00348894, NCT00354094). However, in fibromyalgia, Pfizer reported a small but sustained improvement in overall pain scores (primary outcome) and fatigue (secondary outcome) compared to a placebo.[109]

Dopamine Reuptake Inhibitors

Though classified as a dopamine reuptake inhibitor, bupropion also blocks noradrenaline reuptake transporters. Intrathecal dosing in neuropathic rats increases spinal concentrations of dopamine and noradrenaline, which produces anti-nociception in an α_2 adrenoceptor and D_2 receptor dependent manner.[110] Evidence for efficacy in patients is limited, although a single study reported that 73% of subjects with neuropathic pain studied in their placebo-controlled trial obtained some pain relief with bupropion treatment.[111]

Tetracyclic Anti-depressants

Limited evidence for an analgesic effect of tetracyclic anti-depressants exists. Like the TCAs, the pharmacology of tetracyclics is diverse, but in general, these drugs block noradrenaline reuptake and have little affinity for serotonin and dopamine reuptake transporters. In a crossover study in patients with postherpetic neuralgia, amitriptyline was deemed to be more effective than maprotiline.[112] A few rodent studies have demonstrated that maprotiline,[113] mianserin,[114] and mirtazapine,[115] reverse evoked hypersensitivity in neuropathic models.

Monoamine Oxidase Inhibitors

Renowned for their multiple side effects, drug interactions, and the necessity for a tyramine-free diet when used, monoamine oxidase inhibitors have no place in pain management. Little evidence exists for any analgesic effect.[116]

Safety and Side Effects

The safety of anti-depressants can be considered both from the perspective of normal use (Box 53.2) and in overdose. An analysis of United Kingdom prescriptions provided an interesting insight into the potential dangers of anti-depressants when taken in overdose calculated as the number of deaths per million prescriptions (Table 53.2). It is unclear why the fatality rate for desipramine is higher than other TCAs but suggests that overdose risks should be judged on the data for individual drugs rather than the therapeutic class.[117] In

• BOX 53.2 Anti-depressants: Safety and Side Effects

Weight - Weight gain is common with anti-depressants. When they are used for the treatment of depression, mood alteration may have an effect on appetite and wellbeing. TCAs are more likely than SSRIs to cause weight gain.[122]
Cholinergic-type side effects - including dry mouth, sedation, and urinary retention, may also complicate TCA use.
Risk for falls - A study of United States veterans showed that of 2212 patients with hip fractures, 70% had taken medication before the fracture, which may have contributed to their fall. Patients were twice as likely to have taken a TCA or SSRI as a matched control.[123]
Use in pregnancy - anti-depressant usage has been associated with increased risk of cardiac malformations, preterm births and neonatal respiratory distress.[124]
Automobile Driving - After acute dosing of sedating anti-depressants (e.g. amitriptyline, imipramine, doxepin, mianserin), a measure of driving ability gave results comparable to those of individuals whose blood alcohol concentration was 0.8 mg/mL.[125] It was also noted that concomitant use of a benzodiazepine with an anti-depressant makes driving impairment significant. When SSRIs are considered, no impairment in driving ability has been noted.[126] Consequently, when a TCA is given, the patient should be warned to avoid driving until stabilization with a fixed dose of the TCA has occurred.
SSRIs and NSAIDs - A study of 15,445 new users of anti-depressants with or without the use of nonsteroidal anti-inflammatory drugs (NSAIDs) reported that in the 691 individuals given TCAs who were not taking NSAIDs, the incidence of peptic ulcer drug request was 0.051%. In the SSRI-only group (1181 subjects), the incidence was 1.2%. When an SSRI was taken with an NSAID (86 subjects), the incidence of peptic ulcer drug request was 12.4% instead of 2.5% in the TCA-NSAID cohort. This would suggest that some caution needs to be taken when SSRIs are given to patients taking NSAIDs.[127]

TABLE 53.2 Numbers of Deaths per Million Prescriptions of Anti-depressants (in the United Kingdom)

	Drug	Deaths per million prescriptions (95% confidence interval)
TCAs	Desipramine	200.9 (92.0–381.6)
	Dothiepin	53.3 (50.5–56.1)
	Amitriptyline	38.0 (35.5–40.5)
	Imipramine	32.8 (27.0–39.5)
	Doxepin	25.2 (18.0–34.3)
	Trimipramine	16.5 (11.7–22.5)
	Clomipramine	12.5 (9.4–16.3)
	Nortriptyline	5.5 (2.2–11.4)
	Lofepramine	1.3 (0.6–2.4)
	Butriptyline	0 (0–3372)
	Iprindole	0 (0–1218)
	Protriptyline	0 (0–39.2)
SNRIs	Venlafaxine	13.2 (9.2–18.5)
	Nefazodone	0 (0–6.4)
SSRIs	Fluvoxamine	3.0 (0.3–10.9)
	Citalopram	1.9 (0.6–4.5)
	Sertraline	1.2 (0.5–2.4)
	Fluoxetine	0.9 (0.5–1.4)
	Paroxetine	0.7 (0.4–1.3)
NRIs	Reboxetine	0 (0–21.1)

NRIs, Noradrenaline reuptake inhibitor; *SNRIs*, serotonin-noradrenaline reuptake inhibitors; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic anti-depressants.

Data from Buckley and McManus. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ.* 2002;325(7376):1332–3.[117]

terms of overall comparative tolerability, it would be expected that the newer anti-depressants would be tolerated better than the TCAs. In a meta-analysis reviewing the tolerability of TCAs and SSRIs (when used for the treatment of depression), the number needed to harm (NNH)—in this case, the number of subjects receiving the treatment—for one subject to need to drop out because of side effects was calculated to be 4-30 for TCAs and 20-90 for SSRIs.[118] Similarly, in neuropathic pain, the NNH for TCAs was 13.4, and for SNRIs the NNH was 11.8.[50] For SNRIs, in trials for neuropathic pain, the dropout rates for milnacipran (28%) appear to be higher than for duloxetine (4%-19%) and venlafaxine (9%).[119] The most common adverse effects associated with duloxetine were nausea, dizziness, somnolence, and constipation, which were present in up to 30% of patients.

Conclusion

There is extensive evidence that anti-depressant drugs that block both reuptake of serotonin and noradrenaline can be highly effective for a subset of patients with neuropathic pain. An inherent drawback of the older trials is that drug effects on different types of pain were not evaluated but only showed whether patients with different types of pain achieved pain relief in general. The NNT values of the more recent duloxetine trials tend to be higher than the older TCA trials and reflect an increase in the placebo response over time.[120] Patients with neuropathic pain have been stratified according to their quantitative sensory testing profiles and broadly fall into three categories referred to as the mechanical phenotype, thermal phenotype, and sensory loss group.[27] These sub-groups have been hypothesized to represent surrogate sensory biomarkers of underlying pathophysiologic mechanisms. Concerning sensory profiles, *post hoc* analysis of clinical trials revealed that patients with sensory gain were more likely to benefit from imipramine treatment than those with sensory loss.[85] Other mechanism-based approaches to stratifying patients include exacerbated temporal summation (spinal amplification) or loss of CPM (diminished descending pain control).[121] Impaired CPM appears to be a much more reliable predictor of analgesic response to duloxetine,[23] and this approach could be applied to other anti-depressants with similar mechanisms of action. Although this chapter has focused primarily on neuropathic pain, similar sensory phenotypes have been described in osteoarthritis and fibromyalgia, and the same principles would apply.

Key Points

- Anti-depressants can be effective for treating neuropathic pain independently of their actions on comorbid depression.
- The analgesic effects tend to occur more rapidly and at lower doses than those used for treating depression.
- The primary mechanism of action is through a block of monoamine reuptake in descending modulatory pathways. However, many TCAs have an additional affinity for monoaminergic receptors, which can contribute to their analgesic effects. Side effects can also be attributed to a block of histaminergic and cholinergic receptors.
- Duloxetine and amitriptyline are considered first line therapies for neuropathic pain (NeuPSIG recommendation[50]), though duloxetine is often preferred because of a better side effect profile.
- Low CPM represents a surrogate measure of dysregulated descending modulation in neuropathic pain. CPM could be valuable for mechanism-led treatment selection as low CPM values correlate with the analgesic effects of duloxetine.
- There is little compelling evidence supporting the use of SSRI, noradrenaline reuptake inhibitors, dopamine reuptake inhibitors, tetracyclics, and monoamine oxidase inhibitors for the treatment of neuropathic pain.

Suggested Readings

Bannister K, Dickenson AH. The plasticity of descending controls in pain: Translational probing. *J Physiol*. 2017;595(13):4159–66.

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Adjunct Medications for Pain Management

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Treatment of chronic pain involves understanding the delicate interplay of nociceptive, neuropathic, and nociplastic mechanisms involved in any given pain syndrome's pathophysiology. Research into the underlying pathways for chronic pain has provided the mechanistic basis to utilize numerous non-opioid medications to treat chronic pain disorders. Non-opioid medications, often referred to as adjuvant medications, can take the form of amine reuptake inhibitors, such as the serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic anti-depressants (TCAs); neuronal membrane stabilizers, such as the sodium and calcium channel–blocking anti-convulsants; nonsteroidal anti-inflammatory drugs (NSAIDs); topical analgesics; muscle relaxants; transient receptor potential vanilloid 1 (TRPV1) receptor agonists; N-methyl-D-aspartic acid (NMDA) receptor antagonists; opioid receptor antagonists; and botulinum toxin. The use of NSAIDs, topical analgesics, SNRIs, TCAs, and muscle relaxants in chronic pain disorders are described in other chapters in this text. For this chapter, we will discuss the use of neuronal membrane stabilizers, TRPV1 agonists (capsaicin), NMDA antagonists (ketamine), opioid receptor antagonists (low dose naltrexone), and botulinum toxin, along with data associated with their use for chronic pain management.

Membrane Stabilizers

Alterations in the functioning of sodium and calcium channels have been well-described in the literature regarding the pathophysiology of many chronic pain syndromes.[1,2] Clinically available agents that act on these ion channels include the membrane stabilizing agents typically used to treat epilepsy. Many of these agents have been tried with varying success in patients with pain. Multiple classes of medications that fall under the membrane stabilizer classification are beneficial in treating pain (Table 54.1). These agents include antiepileptic/anti-convulsants, local anesthetics, TCAs, and antiarrhythmic medications. As a group, they inhibit the development and propagation of ectopic neuronal discharges. The primary agents from this adjuvant drug class used to treat chronic pain include antiepileptic/anti-convulsants, local anesthetics, and the TCAs. TCAs are discussed in a separate chapter and not covered here. Gabapentin and pregabalin, also anti-convulsants, are discussed separately under calcium channel modulators because their mechanism of action differs from that of the other membrane stabilizing agents.

Calcium Channel Modulators

Calcium channel modulators are widely used non-opioid medications for chronic pain and are first line treatment agents for many neuropathic and nociplastic chronic pain conditions.[3] The intracellular free calcium ion concentration is only 1 in 10,000 that of the extracellular environment, and influx of calcium through calcium channels has important depolarizing effects on neurons. Voltage-gated calcium channels can be divided into high-voltage-activated (HVA) and low-voltage-activated (LVA) channels. Electrophysiologic characteristics allow division into HVA and LVA channels, depending on the threshold of activation. The HVA group is further divided into types L, P/Q, N, and R.[4] These groups require large membrane depolarization and are mainly responsible for the entry of calcium and release of neurotransmitters from presynaptic nerve terminals. Low-voltage channels, such as the T-type, regulate firing by participating in bursting and intrinsic oscillations. The spike and wave discharges from the thalamus with absence seizures are dependent on T-type calcium channels; these discharges are inhibited by valproic acid or ethosuximide. The N-type HVA calcium channels are thought to be primarily responsible for the release of neurotransmitters at synaptic junctions and become inactivated rather quickly. The P/Q-type calcium channel is so named because it was first described in the Purkinje cells of the cerebellum. The T-type channel, named after the transient current elicited, starts to open with weak depolarization, near resting potential. L-type channels are found in high concentration in skeletal muscle and in many other tissues, such as neuronal and smooth muscle, where it has been most studied. The voltage-gated calcium channel is composed of five polypeptide subunits and is the target of many drugs. Calcium channels consist of an α protein, along with several auxiliary subunits; the α protein forms the channel pore.

The calcium channel modulators that are used to treat chronic pain, such as gabapentin and pregabalin, bind to the $\alpha_2\delta$ subunit of L-type voltage-gated calcium channels, and such binding results in decreased release of glutamate, norepinephrine, and substance P.[5] Though structurally derived from the inhibitory neurotransmitter γ-aminobutyric acid (GABA), neither gabapentin nor pregabalin bind to or have activity at the GABA receptor. They also do not affect the uptake or metabolism of GABA.

TABLE 54.1 Membrane Stabilizers for Pain

Membrane Stabilizer	Mechanism	Side Effects
Carbamazepine	Na channel blockade	Sedation, dizziness, gait abnormalities, hematologic changes
Oxcarbazepine	Na channel blockade	Hyponatremia, somnolence, dizziness
Lamotrigine	Stabilizes slow Na channel; suppress the release of glutamate from presynaptic neurons	Rash, dizziness, somnolence
Gabapentin/pregabalin	Binds to $\alpha_2\delta$ subunit of voltage-gated Ca channel	Dizziness, sedation
Valproic acid	Na channel blockade; increases GABA	Somnolence, dizziness, gastrointestinal upset
Topiramate	Na channel blockade; potentiates GABA inhibition	Sedation, kidney stones, glaucoma
Mexiletine	Na channel blockade	Nausea, blurred vision
Lacosamide	Na channel blockade	Dizziness, nausea, double vision, headache

GABA, γ-aminobutyric acid.

Gabapentin (Neurontin, Gralise, Horizant)

Gabapentin is a non-opioid medication that has been ubiquitously used for chronic pain management. The standard initial dose of gabapentin is dependent on the particular gabapentin formulation used. For the first available preparation of gabapentin (Neurontin), it is 100 to 300 mg daily. Although the United States Food and Drug Administration (FDA)-approved therapeutic dose of this preparation for the treatment of postherpetic neuralgia (PHN) (the only chronic pain condition for which this preparation is FDA-indicated) is 1800 mg, many clinicians will start with a lower dose with a gradual increase to a maximum of 3600 mg/day administered in three divided doses as tolerated (Table 54.2). To minimize the consequence of certain adverse effects such as sedation and dizziness, the initial dose is often given at bedtime. After two to five days, the dose is increased to 300 mg twice daily and, after another two to five days, to 300 mg three times daily after that. Then the dose can be increased by 300 to 600 mg every few days as tolerated until an effective dosage is obtained, the maximum daily dose is reached, or side effects appear. A gastric-retentive formulation of gabapentin (Gralise) has also been approved by the FDA for PHN. It is intended to provide a simpler dosing paradigm than needed with the traditional generic gabapentin through the use of a polymer-based technology that allows gastric retention of the pill for extended delivery of the active medication. Another formulation of gabapentin, gabapentin enacarbil (Horizant), was developed and initially approved to treat restless legs syndrome. It is an actively transported prodrug form of gabapentin that allows twice-a-day dosing because of increased stability in bioavailability compared to the standard formulation of gabapentin. In a randomized controlled trial (RCT), this prodrug formulation was also found to be effective in the treatment of PHN when given twice per day.[6] This drug is approved by the FDA to treat PHN and restless leg syndrome.

The primary dose-limiting side effects of gabapentin are fatigue, somnolence, and dizziness, which are often attenuated by gradual dose titration. Although gabapentin has few drug interactions, a reduced dosage is necessary for patients with renal insufficiency. However, starting dosages of gabapentin often do not provide immediate pain relief, and the slow titration requirements may result in adequate pain relief taking up to two months to achieve when given as immediate-release gabapentin. When given as the extended-release formulation, therapeutic doses can be reached in approximately two weeks.

Gabapentin has uses in multiple chronic pain conditions. Studies have been performed on patients being treated for PHN, complex regional pain syndrome (CRPS), painful diabetic neuropathy (PDN), and other forms of neuropathic pain (NP) and pain of controversial etiology, including fibromyalgia and opioid-induced hyperalgesia.[7–9] A meta-analysis of 5914 participants in 37 studies found substantial benefits (at least 50% pain relief or "very much improved" on the patient global impression of change [PGIC] scale) for patients with PHN and PDN. Common side effects across the entire meta-analyzed population included dizziness (19%), gait disturbance (14%), somnolence (14%), and peripheral edema (7%). Among 2260 patients with PHN from eight studies, 32% of subjects had a substantial response to gabapentin ≥1200 mg daily compared with 17% of subjects receiving placebo (RR 1.8 [95% confidence interval [CI] 1.5 to 2.1]; number needed to treat (NNT) 6.7 [5.4 to 8.7]). When "moderate benefit" (at least 30% pain relief or PGIC of "much improved" or "very much improved") was examined, 46% of PHN participants met these criteria compared with 25% of those taking placebo (RR 1.8 [95% CI 1.6 to 2.0]; NNT 4.8 [4.1 to 6.0]). Evidence for both of these outcomes was graded as moderate quality. The same meta-analysis found that among 1277 PDN patients across six studies, 38% receiving gabapentin ≥1200 mg/day derived substantial benefit compared with 21% of subjects receiving placebo (RR 1.9 [95% CI 1.5 to 2.3]; NNT 5.9 [4.6 to 8.3]). Similarly, 52% of subjects receiving gabapentin had moderate benefit, while 37% of those receiving placebo did (1439 total participants across seven studies; RR 1.4 [95% CI 1.3 to 1.6]; NNT 6.6 [4.9 to 9.9]). Evidence was again graded as moderate quality. Of note, very limited data are available for gabapentin use in other neuropathic pain conditions such as nerve injury, spinal cord injury, and radicular leg pain despite this medication being commonly used for these indications.[10] Other meta-analyses have looked at gabapentin use in phantom limb pain, showing a mean Numerical Rating Scale (NRS) difference of –1.16 (95% CI –1.94 to –0.38) for gabapentin compared with placebo in a small total sample of 43 subjects,[11] and in chronic low back

TABLE 54.2 Dosing Recommendations for Neuropathic Pain

Membrane Stabilizer	Initial Dosage	Titration	Max Therapeutic Dosage
Carbamazepine	100–200 mg BID	Increase by 200 mg increments gradually	1200 mg QD
Oxcarbazepine	600 mg daily BID	Increase by 300 mg	1200–1800 mg TID
Lamotrigine	25–50 mg QHS	Increase by 50 mg every one to two weeks	300–500 mg QD
Gabapentin*	100–300 mg QHS	Increase by 100–300 mg or 100–300 mg TID every one to seven days as tolerated	3600 mg (1200 TID)
Gabapentin GR	300 mg QHS	Day one, 300 mg; day two, 600; days three to six, 900; days seven to ten, 1200; days 11–14, 1500, then 1800	1800 mg QHS
Pregabalin*	50 mg TID or 75 mg BID	Increase to 300 mg daily after three to seven days, then by 150 mg/day every three to seven days as tolerated	600 mg QD (200 mg TID or 300 mg BID)
Valproic acid	250 mg BID	Increase by 250 mg weekly	500 mg BID
Topiramate	50 mg QHS	Start at 50 mg BID after one week, then increase 100 mg BID after seven days	100 mg BID
Mexiletine	150 mg QD	Increase to 300 mg in three days and then 600 mg	Maximum: 10 mg/kg daily

*Reduce if impaired renal function.

BID, twice daily; *QHS*, at bedtime; *QD*, daily; *TID*, three times daily.

pain (cLBP), unsurprisingly showing no significant improvement in pain compared with placebo in 185 subjects (mean NRS difference –0.22 [95% CI –0.5 to 0.07]), with low quality evidence.[12] Overall, most guidelines for the treatment of NP include gabapentin as a first line agent.[13]

Recent attention has focused on the potential for misuse and use disorder related to gabapentin, as well as the risk of morbidity and mortality when this medication is co-prescribed with opioids. A systematic review of 59 studies examining gabapentinoid misuse and abuse found a 1.6% prevalence of abuse among the general population but prevalence ranging from 3%-68% among opioid abusers; overall risk factors for abuse included a history of substance misuse, particularly opioids, and psychiatric comorbidities. Prescribers should exercise caution with gabapentin in these populations.[14] A population-based nested case-control study of 1256 opioid users who died of opioid-related causes and 4619 opioid users found that opioid and gabapentin coadministration significantly increased the odds of opioid-related death compared with opioid use without gabapentin (adjusted odds ratio 1.49, 95% CI 1.18 to 1.88).[15] The FDA recently added a black box warning to gabapentin (as well as pregabalin, discussed below), cautioning that respiratory depression and sedation may occur in elderly patients or those with respiratory conditions receiving gabapentinoids concurrently with central nervous system (CNS) depressants such as opioids and benzodiazepines.[16]

Few studies have looked at the use of gabapentin on cLBP. One study by Atkinson et al. investigated gabapentin versus inert placebo for cLBP and found that within each treatment arm, there was statistically significant reductions in pain. However, when comparing gabapentin to placebo, there was no statistically significant difference in pain relief between the two groups.[17]

Gabapentin has been reported as useful in the treatment of fibromyalgia. However, only one rigorous RCT has been published investigating gabapentin versus placebo for this condition. In this study by Arnold et al. 150 patients were randomized to either placebo or gabapentin (titrated to doses of 1200–2400 mg/day) for 12 weeks.[18] Results showed that gabapentin-treated patients had significantly greater improvement in average pain scores of a modest effect.

Pregabalin (Lyrica)

Like gabapentin, pregabalin is used to treat chronic pain and acts by binding to the $\alpha_2\delta$ subunit of L-type voltage-gated calcium channels, which results in decreased neuronal excitation. Pregabalin is approved by the FDA for the treatment of PHN, PDN, fibromyalgia, and spinal cord injury-associated pain. Initial pregabalin dosing is 150 mg/day given in two or three divided doses or 25 to 50 mg given at bedtime in elderly patients. Upward dose titration can be completed after three to seven days to 300 mg/day and subsequently increased to a maximum dose of 600 mg/day within two weeks of initiation. Similar to gabapentin, dosing of pregabalin must be decreased in patients with reduced kidney function. Advantages of pregabalin over gabapentin include a more rapid onset of pain relief, linear pharmacokinetics with low inter-subject variability,[19] fewer dose-related side effects, thereby allowing faster upward dosage titrations, and twice daily versus three times a day dosing. Additionally, a maximum benefit often occurs after two weeks of treatment at target doses of 300 to 600 mg/day versus up to two months in gabapentin-treated patients. The advantage of pregabalin is its early response and favorable side effect profile.[20] The most common adverse effects include somnolence and dizziness, and they occur more frequently with higher doses. When discontinuing pregabalin, it should be tapered down gradually over at least one week to minimize symptoms, including insomnia, nausea, headache, and diarrhea.

As with gabapentin, pregabalin's efficacy has been established in patients with PHN and PDN. One meta-analysis included

11,906 patients from 45 studies.[21] Among subjects with PHN, subjects taking pregabalin 300 mg daily were more likely to experience ≥50% pain relief (32% vs. 13%; RR 2.5 [95% CI 1.9 to 3.4]; NNT 5.3 [3.9 to 8.1] among 713 subjects across four studies) and ≥30% pain relief (50% vs. 25%; RR 2.1 [95% CI 1.6 to 2.6]; NNT 3.9 [3.0 to 5.6] among 589 subjects across three studies) compared with those taking placebo. A dose-response relationship was observed among this population: Subjects administered pregabalin 600 mg daily compared with those given placebo were more likely to attain ≥50% pain relief (41% vs. 15%; RR 2.7 [95% CI 2.0 to 3.5]; NNT 3.9 [3.1 to 5.5] among four studies with 732 participants) and ≥30% pain relief (62% vs. 24%; RR 2.5 [95% CI 2.0 to 3.2]; NNT 2.7 [2.2 to 3.7]) in three studies with 537 participants. Evidence for all PHN analyses was graded as moderate quality.

For PDN, subjects administered pregabalin 300 mg daily compared with placebo were more slightly more likely to obtain ≥50% pain reduction (31% vs. 24%; RR 1.3 [95% CI 1.2 to 1.5]; NNT 22 [12 to 200] among 2931 participants in 11 studies) and ≥30% pain reduction (47% vs. 42%; RR 1.1 [95% CI 1.01 to 1.2]; NNTB 22 [12 to 200] among eight studies with 2320 participants), and substantially more likely to report "much" or "very much" improved PGIC (51% vs. 30%; RR 1.8 [95% CI 1.5 to 2.0]; NNT 4.9 [3.8 to 6.9] in five studies with 1050 participants). As with PHN, more improvement was observed with the 600 mg daily dose than with 300 mg, with ≥50% pain reduction noted in 41% of those taking this dose compared with 28% of patients taking placebo (RR 1.4 [95% CI 1.2 to 1.7]; NNT 7.8 [5.4 to 14] in five studies with 1015 participants) and ≥30% pain reduction seen in 63% versus 52% on placebo (RR 1.2 [95% CI 1.04 to 1.4]; NNT 9.6 [5.5 to 41]; 611 participants from two studies). In the PDN studies, evidence for the 300 mg daily dose was graded as moderate quality, while evidence for the 600 mg dose was graded as low quality.

Benefit was also seen for pregabalin 600 mg daily dose in mixed or unclassified posttraumatic neuropathic pain: Meta-analysis of 1367 subjects from four studies showed ≥50% pain reduction in 34% of patients taking pregabalin compared with 20% of those taking placebo (RR 1.5 [1.2 to 1.9]; NNT 7.2 [5.4 to 11]; moderate quality evidence) and ≥30% pain reduction in 48% vs. 36% (RR 1.2 [1.1 to 1.4]; NNT 8.2 [5.7 to 15]; low quality evidence).[21] Pregabalin was also more likely to be efficacious than placebo in central neuropathic pain. Among 562 participants in three studies, 26% (vs. 15%) obtained ≥50% pain relief (RR 1.7 [1.2 to 2.3]; NNT 9.8 [6.0 to 28]; low quality evidence) and 44% (vs. 28%) obtained ≥30% pain reduction (RR 1.6 [1.3 to 2.0]; NNT 5.9 [4.1 to 11]; also, low quality evidence). There was no evidence of benefit in HIV neuropathy when 674 subjects in two studies were meta-analyzed (moderate quality evidence) and limited data for other NP conditions, including cancer pain, polyneuropathy, back pain, and sciatica. Except for PHN, a daily pregabalin dose of 150 mg daily was found to be ineffective; clinicians should consider higher doses should therapy at lower doses prove unhelpful. Clinicians should also be cognizant of the potential for misuse, abuse, and respiratory depression with gabapentinoids, as discussed previously in this chapter.

Two studies have investigated pregabalin compared to active control groups, and pregabalin was not found to be superior to opioids[22] or celecoxib[23] for treatment of cLBP. However, celecoxib plus pregabalin was superior to monotherapy in the study by Romano et al.[23]

Many studies have been performed investigating the use of pregabalin for the treatment of fibromyalgia syndrome. Seven RCTs have investigated pregabalin monotherapy at varying doses ranging from 150 to 600 mg/day and were found to have superior pain relief compared to placebo. Arnold et al.[24] and Mease et al.[25] both found that daily total doses of 300/450/600 mg were all superior in pain efficacy to placebo. Crofford et al. found that only 450 mg/day dosing was superior to placebo for pain efficacy (not 150 or 300 mg/day).[26] At doses of 300 or 450 mg/day, Ohta et al. reported superior efficacy of pregabalin over placebo.[27] Arnold et al.[28] and Clair[29] et al. also reported superior efficacy of pregabalin in pooled groups of pregabalin doses (300-450 mg/day) over placebo. Pauer et al. published that only a modest statistically significant effect over placebo was noted at 450 mg/day (not at 300 or 600 mg/day).[30] In a study by Gilron et al. combination therapy of pregabalin plus duloxetine versus placebo or monotherapy was investigated, and the authors reported that combination therapy is superior to placebo and pregabalin monotherapy.[31]

Zonisamide (Zonegran)

Zonisamide is indicated as adjunctive therapy for partial seizures in adults and became available in the United States in 2000. It acts by blocking T-type calcium channels and sodium channels; its action also increases the release of GABA. The initial dose is 100 mg/day for two weeks with increases of 200 mg/week to a target of 600 mg/day. There have been case reports on its usefulness for post-stroke pain and headache. A randomized, double-blind, placebo-controlled pilot study of the efficacy of zonisamide for the treatment of PDN revealed that pain scores on the visual analog scale (VAS) and Likert (psychometric response) scales decreased more in the zonisamide group than in the placebo group. However, these differences did not reach statistical significance.[32] Side effects included ataxia, decreased appetite, rash, and renal calculi (resulting from the carbonic anhydrase inhibitor effect). Zonisamide is contraindicated in those with sulfonamide allergy because it is a sulfonamide derivative, and the drug is approximately 40% bound to plasma proteins. Children have an increased risk for oligohidrosis and susceptibility to hyperthermia. Convincing data for zonisamide's efficacy in other chronic pain syndromes has yet to appear.[33]

Ziconotide (Prialt)

Ziconotide is a ω-conopeptide (previously known as SNX-111) that is administered intrathecally because of its peptidic structure. It is derived from the venom of a marine snail (genus *Conus*). Ziconotide blocks calcium influx into N-type calcium channels in the dorsal horn laminae of the spinal cord, thus preventing afferent conduction of nerve signals. The administration is via an intrathecal infusion pump, and dosing should be started low, at a recommended dose of 2.4 μg/day (0.1 μg/h). Because of a lag time, it should be titrated up slowly at intervals of no more than two to three times per week to a recommended maximum of 19.2 μg/day.[34] Ziconotide does not cause tolerance, dependence, or respiratory depression, and adverse effects primarily involve the CNS and range from dizziness, ataxia, confusion, and headache to frank psychosis and suicidal ideation.

Ziconotide monotherapy's effect on chronic NP has been meta-analyzed from three RCTs with a total of 586 subjects. The pooled OR of ≥30% pain reduction with ziconotide vs. placebo was 2.77 (95% CI 1.37 to 5.59).[35] Serious adverse events were common in the included studies, but evidence shows that these

may be decreased by slow titration.[36] A prospective multicenter observational registry of ziconotide use (either as monotherapy or with other intrathecal medications) observed ≥30% pain reduction in 17.4% of patients at 12 weeks and 38.5% of patients at 18 months. Nearly all patients included in the registry experienced side effects, including 22.6% with confusion.[37]

The role of ziconotide in the management of chronic pain has yet to be fully elucidated. Currently, ziconotide is approved for the management of severe chronic pain in patients in whom intrathecal therapy is warranted and who are intolerant of or refractory to other treatments, including intrathecal opioids, local anesthetics, and α-adrenergic agonists. However, this medication should be used cautiously because of its poor side effect profile. Particular attention should be paid to patients with preexisting psychiatric disease.

Sodium Channel Blockers

Sodium channel blockers are used as primary therapy or adjunctive treatment of neuropathic pain syndromes such as trigeminal neuralgia (TN), CRPS, PDN, radicular extremity pain, chemotherapy-induced peripheral neuropathy, and PHN. When using these agents, as with all membrane stabilizers, it is crucial to be knowledgeable of the proper dosages, toxicities, and their effects when coadministered with other drugs. As a general rule, the dose should be titrated to patient comfort within safety standards.

When neurons are depolarized and approaching an action potential, the voltage-gated sodium channels quickly change conformation in response and permit the flow of sodium ions. Activation of sodium channels (and other voltage-gated ion channels) derives from the outward movement of charged residues because of an altered electrical field across the membrane. Sodium channels play an essential role in the action potentials of neurons and other electrically excitable cells. The flow of sodium ions is terminated by the inactivation of the channel in a few milliseconds (fast inactivation). Sodium channels can cycle open and close rapidly, which may result in seizures, neuropathic pain, or paresthesia. The structure of the channel is essentially a rectangular tube, with its four walls formed from four subunits, the four domains of a single polypeptide. A region near the N-terminus protrudes into the cytosol and forms an inactivating particle. It has been demonstrated that a short loop of amino acid residues, acting as a flap or hinge, blocks the inner mouth of the sodium channel and results in fast inactivation.[38] The highly conserved intracellular loop is the inactivating gate that binds to the intracellular pore and inactivates it within milliseconds. Site-directed antibody studies against this intracellular loop have prevented this fast inactivation.

The voltage-gated sodium channel can be divided into an α subunit and one or more auxiliary β subunits. At least nine α subunits have been functionally characterized—Nav1.1 through Nav1.9.[39] The sodium channels 1.2, 1.8, and 1.9 are preferentially expressed on peripheral sensory neurons, where they are important in nociception and may be a future target for channel-specific analgesics.[40] Seven of the nine sodium channel subtypes have been identified in sensory ganglia, such as the dorsal root ganglia and trigeminal ganglia. Nav1.7 is also present in large amounts in the peripheral nervous system. Nav1.2 is expressed in unmyelinated neurons, and Nav1.4 and Nav1.5 are muscle sodium channels. Sodium channel mutations that result in well-recognized syndromes have been described. A mutation in the gene encoding Nav1.4 is responsible for hyperkalemic periodic paralysis, and an inherited long QT syndrome can be caused by a mutation in the gene encoding Nav1.5. Mutations in *SCN9A*, which encodes Na 1.7, have been associated with several pain disorders: Primary erythromelalgia and paroxysmal extreme pain disorder are caused by gain-of-function variants. In contrast, congenital insensitivity to pain is caused by a loss-of-function variant.

Increased expression of sodium channels has been demonstrated in peripheral and central sensory neurons in patients with chronic pain; it is one mechanism for the observed hyperexcitability of pain pathways.[41] Anti-convulsants that modulate the gating of sodium channels include phenytoin, lamotrigine, carbamazepine, oxcarbazepine, and zonisamide, with some evidence for topiramate and valproic acid. It is important to note that at clinical concentrations, the sodium channel is only weakly blocked when hyperpolarized. When the neuronal membrane is depolarized, there is a much greater inhibition of the channel. The binding of the channel by anti-convulsants is slow in comparison to local anesthetics. The slow binding of anti-convulsants ensures that the kinetic properties of normal action potentials are not altered. Generally, anti-convulsants have no role in the treatment of acute pain, although they have demonstrated efficacy in chronic pain conditions. Interestingly, local application of phenytoin and carbamazepine has an antinociceptive effect that is more potent than lidocaine.[42] It has been demonstrated that phenytoin, carbamazepine, and lamotrigine bind to a common recognition site on sodium channels, probably as a result of their two phenol groups, which act as binding elements.[43] At normal resting potentials, these medications have little effect on action potentials. Besides the fast current of the open channel, there is also a persistent sodium current. This current, carried by persistent openings, is a small fraction of the fast current but may have an important role in regulating excitability. There is evidence that several anti-convulsants, such as phenytoin, valproate, and topiramate, also act by blocking the persistent sodium current.

Phenytoin (Dilantin)

Besides the widespread use of phenytoin for seizures, it was the first anti-convulsant to be used for NP, with a 1940s report on its use for TN. Phenytoin is known for its nonlinear metabolism, which is manifested as marked increases in plasma level with small increases in dose after saturation of metabolism. Around 95% of a phenytoin dose is excreted as metabolites from the cytochrome P-450 system. The initial dosage of phenytoin is 100 mg two to three times daily. It has primarily been used for the treatment of diabetic neuropathy. However, because of the mixed results of its efficacy and high side effects and medication interaction profile, it has fallen into disuse. Phenytoin provides pain relief by blocking sodium channels, thereby preventing the release of excitatory glutamate and inhibiting ectopic discharges.

Intravenous phenytoin has been studied in the chronic pain setting, but data are limited. A systematic review and meta-analysis did not identify any studies warranting inclusion.[44] Side effects of phenytoin include slowing of mentation and somnolence, with nystagmus and ataxia occurring in some patients. Among the epileptic drugs, phenytoin is unique in the development of facial alterations, including gum hyperplasia and coarsening of facial features. Fosphenytoin, an intravenously administered prodrug that converts to phenytoin, is used by some to avoid long dosing intervals or initial burning at the injection site.

Phenytoin activates the cytochrome P-450 enzyme system in the liver, and hence careful assessment of co-therapy is warranted. For example, phenytoin decreases the efficacy of methadone, fentanyl, tramadol, mexiletine, lamotrigine, and carbamazepine.

As a result, dosages of these medications should be adjusted accordingly. Coadministration with anti-depressants and valproic acid could lead to an increased blood concentration of phenytoin, thereby lowering the subsequent doses required for effect in patients. Most would not use phenytoin for the treatment of NP except perhaps in refractory situations.

Carbamazepine (Tegretol)

Carbamazepine has been used in the United States since the 1980s to treat partial and generalized tonic-clonic seizures. Interestingly, it was *first* approved by the FDA for the treatment of TN, not for epilepsy. Besides its anti-convulsant and TN indications, it is used frequently for bipolar disorder. It was one of the first anti-convulsants studied for the relief of NP. The analgesic properties of carbamazepine were first reported in 1962.[45] It is chemically related to the TCAs; reports have included studies of its use for PHN, PDN, post-stroke pain, and pain in Guillain-Barré syndrome. The initial dosage of carbamazepine is 100 to 200 mg twice daily, titrated to effect, with typical dose ranges of 300 to 1200 mg/day administered in two divided doses. Common maintenance doses are 600 to 800 mg.

Common side effects include drowsiness, dizziness, nausea, and vomiting, which can often be limited by slow titration. Carbamazepine is associated with very deleterious side effects, including pancytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Carbamazepine is considered the pharmacologic treatment of choice for TN. Although the pathology of this severe neuropathic facial pain in one of the distributions of the trigeminal nerve has not been fully determined, the majority of cases are thought to be caused by compression of the trigeminal nerve at the pontine origin of the nerve by an aberrant loop of an artery or vein. Despite (and likely because of) its longstanding history of use for this condition, high quality evidence for the efficacy of carbamazepine in TN was found lacking in a recent meta-analysis. Only two small placebo-controlled studies of short duration from the 1960s were included, with an overall RR of 6.02 (95% CI 2.82 to 12.85).[46] However, societal guidelines emphasize the excellent treatment response seen in four such small studies, with 58% to 100% of patients obtaining meaningful pain relief compared with 0% to 40% in placebo groups and an NNT <2.[47] Regardless, TN is a disease process that in many patients is challenging to treat completely, with multiple agents often being required.

Carbamazepine has also been investigated for use in other chronic NP states, with a similar lack of high quality evidence. Combined meta-analysis of four studies including 188 patients with TN, PDN, and post-stroke pain calculated a RR of 6.5 (95% CI 3.4 to 12) with an NNT of 1.9 (95% CI 1.6 to 2.5) for ≥50% reduction in pain, with the caveat that studies were small and of short duration.[46] Importantly, patients maintained on carbamazepine therapy should have blood tests done every two to four months because of increased risk for the development of agranulocytosis and aplastic anemia with this agent. Studies have noted that the number needed to harm (NNH) for severe adverse effects was 24 and for minor adverse effects, such as sedation, was three.[47]

Oxcarbazepine (Trileptal)

Oxcarbazepine, the keto-analog of carbamazepine, was developed to preserve the membrane stabilizing effects of carbamazepine while minimizing minor adverse effects such as sedation and serious, life-threatening reactions. A major advantage of oxcarbazepine is that monitoring plasma drug levels and hematologic profiles is not generally necessary. Similar to carbamazepine, oxcarbazepine blocks sodium channels; it does not affect GABA receptors.

Significant hyponatremia (sodium <125 mmol/L) may develop during treatment with oxcarbazepine. This typically occurs during the first three months, with sodium levels normalizing within a few days of discontinuing the drug. Monitoring of sodium levels should be performed when instituting oxcarbazepine therapy. Frequently reported adverse effects of oxcarbazepine include dizziness, somnolence, nausea, and vomiting, which are generally well tolerated; dermatologic adverse effects such as Stevens-Johnson syndrome and toxic epidermal necrolysis have also been infrequently reported.

The superior side effect profile of oxcarbazepine over carbamazepine has led to its increased use. Published guidelines list it as "probably effective" for treating pain from TN based on two moderate quality RCTs showing equal efficacy of oxcarbazepine and carbamazepine in 130 patients, with 88% showing a reduction in pain attacks by 50%.[47] Oxcarbazepine has also been found effective in treating TN in patients who had no positive response to carbamazepine,[48] and physicians should consider substituting one for the other in patients with insufficient analgesic response.[49] Meta-analysis of oxcarbazepine data has identified no appropriate placebo-controlled trials related to TN, and little evidence to support its use in other forms of NP such as PDN, radicular pain, and mixed neuropathy,[50] although a single RCT of 146 patients with PDN did show a significantly greater number of subjects attaining ≥50% pain relief with oxcarbazepine compared with placebo (34.8% vs. 18.2%, RR 1.91 [95% CI 1.08 to 3.39], NNT 6 [95% CI 3 to 41]).[51]

Lamotrigine (Lamictal)

Lamotrigine received FDA approval in 1994; it is used as an adjunctive agent for partial seizures and as monotherapy for partial and generalized seizures. Like other agents discussed in this section, lamotrigine is an agent that blocks sodium channels in actively firing nerves. It has no effect on sensation in the native, normally functioning nervous system. Unique to lamotrigine is the fact that in addition to acting as a sodium channel blocker, the drug prevents the release of glutamate, an excitatory transmitter involved in pain propagation. Adverse events such as dizziness, somnolence, and cognitive impairment occur with lamotrigine.[52] There is little dose-dependent toxicity, so monitoring of laboratory values is not necessary. The most concerning side effect is rash, which occurs more often with rapid titration; it can manifest as Stevens-Johnson syndrome.[53] The risk for rash is similar to that with phenytoin or carbamazepine, 5% to 10%. Enzyme-inducing drugs reduce the serum level of lamotrigine. Lamotrigine has no effect on liver enzymes, is metabolized via glucuronidation, and is 55% protein bound with a half-life of 30 h. It needs slow titration, at least four to six weeks.

Lamotrigine is considered a second-line agent, along with baclofen and gabapentin, to treat TN. Although carbamazepine and oxcarbazepine are generally considered first line therapy for TN, they are not always effective in these patients. Lamotrigine has been investigated in this patient population for use as a coadministered drug and as a substitute for carbamazepine in several small studies with promising results.[54-56] The use of lamotrigine may therefore be considered for carbamazepine- or oxcarbazepine-resistant TN. Lamotrigine has been shown to be minimally effective in the reduction of pain intensity in PDN in two placebo-controlled

RCTs,[57,58] and no change in one.[58] Subjects had no improvement in sleep interference, quality of life, patient reported improvement in pain, or mood and the most common side effect was rash.[57,58] In the positive trials, the minimal effective dose ranged from 400 mg/daily, and pain reduction occurs within six weeks. A meta-analysis of 1511 participants from 11 studies found minimal evidence of efficacy in other NP states such as central post-stroke pain, chemotherapy-induced neuropathic pain, DPN, HIV-related neuropathy, post-spinal-cord-injury pain, and mixed neuropathic pain.[59]

Topiramate (Topamax)

Topiramate has multiple mechanisms of action and is broadly used for seizure disorders. Topiramate blocks voltage-sensitive sodium channels, limits sustained repetitive firing, and binds to GABAA receptors to enhance GABA activity through non-benzodiazepine- and non-barbiturate-related mechanisms. It increases the opening frequency of chloride ion channels in GABAA receptors and can block α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-kainate glutamate receptors by acting as a negative modulator of glutamate at this receptor. Topiramate also reduces the activity of L-type calcium channels and is a carbonic anhydrase inhibitor. Topiramate exhibits linear pharmacokinetics over its dose range and has a half-life of 19 to 25 h. Its oral bioavailability is about 85%, and it is not affected by food. Enzyme-inducing drugs may reduce the serum level of topiramate. Common side effects include paresthesia because of inhibition of carbonic anhydrase, drowsiness, fatigue, and cognitive symptoms. The incidence of nephrolithiasis was 1.5% in clinical trials, and mild weight loss is often noted. The propensity for weight reduction in some patients has led to an investigation of its potential as a weight-reducing agent.[60]

The initial dose is 50 mg at bedtime, with increases to an upper limit of 200 mg twice daily. Studies have demonstrated that pain relief begins to occur at doses of 200 mg/day. Two large trials on migraine prophylaxis with topiramate were published in 2004, and topiramate received FDA approval for this indication.[61,62] Topiramate has been shown to be borderline effective in the reduction of pain intensity, improvement in sleep interference, quality of life, and mood[63] in two RCTs for PDN,[63,64] but ineffective in all domains in two others.[64] In the positive trials, the pain reduction occurs within eight weeks.[63] The most consistent finding in all trials was weight loss. Significantly more subjects lost weight in the topiramate group than placebo control subjects.[63] However, a review of multiple double-blind studies examining the efficacy of topiramate for PDN failed to show significant analgesic benefit,[55] and a meta-analysis of 1684 patients with either PDN or lumbar radiculopathy found a similar lack of efficacy with doses of 200 to 400 mg daily compared with placebo.[65] Few studies have investigated topiramate for cLBP. However, in one placebo-controlled RCT, the effects of topiramate on cLBP compared to inert placebo showed that topiramate was superior to placebo in reducing pain scores.[66] As clear benefit for topiramate in neuropathic pain has not been shown, it may best be reserved as an adjunct for refractory pain management when failure to achieve successful analgesic relief has occurred with other membrane stabilizer agents.

Lacosamide (Vimpat)

Lacosamide is an effective and well tolerated antiepileptic drug that is used as adjuvant treatment of focal-onset seizures uncontrolled by other agents.[67] Although it has not been compared directly with other adjuvant treatment options, its different mechanism of action and favorable safety profile make this antiepileptic agent a valuable addition to the treatment options available. The primary action of lacosamide is an enhancement of slow inactivation of voltage-gated sodium channels without any apparent interaction with fast inactivation, a mechanism that differs from that of other sodium channel-blocking membrane stabilizers. In addition to treating epilepsy, lacosamide has been found to be beneficial in the treatment of PDN. A meta-analysis including 1863 patients with PDN from five studies found moderate quality evidence that a 400 mg daily dose is beneficial, with an NNT compared with placebo between 10 and 12.[68] Consequently, lacosamide may be considered as an adjunct in difficult-to-treat neuropathic pain.

GABAergic Medications

Valproic Acid (Depakote)

First synthesized in 1882, valproate became available in the 1960s as an antiepileptic agent and received FDA approval in 1978 as an immediate-release formulation.[69] The drug has a broad spectrum of use for seizure disorders, including absence seizures, and is now also used extensively by psychiatrists for mood disorders. The exact molecular mechanisms responsible for its clinical effects are unknown. Catabolism of GABA is inhibited, and the synaptic release of GABA is increased. There are conflicting reports in the literature regarding the efficacy of this agent for NP, although studies have demonstrated that it is effective as migraine therapy at dosages of 750 mg/day for three months.[70] A meta-analysis identified three small placebo-controlled RCTs of valproic acid for NP: two in PDN and one in PHN. Two of the three showed statistically significant (albeit mild) improvements in pain.[71] Side effects include gastrointestinal upset, somnolence, and dizziness. The exact role of valproic acid in the armamentarium of the pain practitioner is yet to be elucidated, but given the superior evidence available for other medications, it should not be considered for initial therapy of NP.[72]

Diazepam (Valium), Lorazepam (Ativan), Clonazepam (Klonopin)

Benzodiazepines, such as diazepam, lorazepam, and clonazepam, facilitate the actions of GABA in the CNS because of their binding to the GABAA receptor. The side effects of drowsiness and ataxia and the development of tolerance to the antiseizure effect limit the usefulness of benzodiazepines for chronic use. Clonazepam is sometimes used for chronic neuropathic pain but has limited evidence to support this.[73]

Although benzodiazepines are frequently prescribed for multiple pain syndromes, there is little, if any, evidence of their benefit as pain therapy, and they are more commonly associated with adverse events, particularly when co-prescribed with opioids.[74]Aside from recognized use for two rare pain conditions (burning mouth syndrome and stiff-person syndrome), benzodiazepines do not appear to have a risk-benefit ratio that warrants use as analgesics for chronic pain.[75]

Local Anesthetics

Local anesthetics are used in NP states to block the aberrant firing of abnormal nerves, although they also block normally conducting (non-nociceptive) nerves. As a group, they are effective in the treatment of PHN, TN, radiculopathies, and peripheral neuropathies.

Lidocaine

Intravenous lidocaine has been shown to have modulatory effects not only on sodium channels but also on potassium and calcium channels, muscarinic receptors and NMDA receptors, the glycinergic system, and G-protein-coupled receptors.[76] The anti-inflammatory properties of systemic lidocaine are also being recognized.[77] Intravenous lidocaine has been the focus of several studies for NP; meta-analysis has shown significant superiority to placebo, with a weighted mean difference in VAS of –11 mm (95% CI –17 to –5 mm) among 373 subjects.[78] However, while another recent meta-analysis observed a similar reduction in NP following individual lidocaine infusions (500 patients; weighted mean VAS difference –11.9, 95% CI –16.8 to –7), it did not show long-term efficacy for multiple lidocaine infusions over a four week period in decreasing NP (110 patients; weighted mean VAS difference –0.96; 05% CI –2.02 to 0.11).[79] Consequently, such infusions may be better suited to the acute rather than chronic settings. The typical intravenous infusion dose of lidocaine is 0.5 to 2 mg/kg/h. Side effects include dizziness, blurred vision, and seizures, which typically occur at a plasma level of 10 mg/mL.[80] Given that lidocaine is an antiarrhythmic, bradycardia and cardiac depression (present at a 20- to 25 mg/mL plasma concentration) are potential risks with this agent. Therefore electrocardiographic studies are indicated for long-term or high-dosage use of lidocaine, as is close monitoring.

A patch formulation of 5% lidocaine (Lidoderm) is available in a topical preparation, as is a 1.8% lidocaine topical system (ZTLIDO). Approved by the FDA for PHN, it has also proved to be of benefit in patients with various other types of neuropathic pain, including PDN, post-thoracotomy pain, intercostal neuralgia, and meralgia paresthetica.[81] Few studies have been performed investigating the use of lidocaine patches for musculoskeletal pain conditions. In a study investigating the use of lidocaine patch in cLBP, 30 patients were randomized to either a 5% lidocaine patch or placebo patch.[82] After two weeks of use, both lidocaine and placebo patch groups reported a greater than 50% decrease in pain, suggesting that there may be no independent efficacy of 5% lidocaine patch for cLBP. In myofascial pain syndrome (MPS), one RCT compared the effects of a topical lidocaine patch (total daily dose 350 mg), placebo patch, and injection of 0.5% bupivacaine over one painful trigger point for a total of four days.[83] This study found that lidocaine patches and local anesthetic infiltration were effective for pain and superior to placebo in the short-term for patients with MPS. In another RCT, it was reported that a 5% lidocaine patch used for 14 days in cervical MPS might be superior to placebo, but the significant difference between the two groups may have been skewed by an unexpected increase in pain in the placebo patch group.[84] While the evidence for lidocaine use in NP is strong, as evidenced by the FDA approval for lidocaine patch for many neuropathic pain syndromes, the evidence is not as strong for musculoskeletal pain conditions. Thus although a 5% lidocaine patch is low-risk and potentially beneficial, it may be prudent to use other agents known to benefit these conditions and only utilize a 5% lidocaine patch in refractory cases.

The eutectic mixture of local anesthetics (EMLA)—composed of prilocaine and lidocaine—has also been advocated for use as a topical local anesthetic. This agent is sometimes used as an adjunct for venipuncture in the pediatric population, but care must be taken with the amount of EMLA cream given to patients to avoid toxicity. Prilocaine is readily metabolized to *O*-toluidine, which can lead to methemoglobinemia. However, if dosages of prilocaine are kept below 600 mg, clinical methemoglobinemia is less likely to develop.

Mexiletine

Mexiletine is an antiarrhythmic and, for pain relief, can be considered an oral analog of lidocaine. Pain physicians may provide intravenous lidocaine for pain management, with monitoring of dose and effect. After receiving a dose of intravenously administered drug, treatment may readily be converted to oral mexiletine. The standard starting dose is 75 to 150 mg/day with a target of 300 to 450 mg/day.

Mexiletine can be used for PDN, thalamic stroke pain, spasticity, allodynia, and myotonia.[85] Meta-analysis of 377 subjects from nine placebo-controlled RCTs showed results for NP similar to lidocaine (weighted mean VAS difference –11 mm; 95% CI –16 to –6 mm).[78] Mexiletine has also been used successfully in patients with the rare Nav1.7 mutation causing erythromelalgia.[86] Common side effects, including somnolence, irritability, blurred vision, and nausea, and vomiting, limit the utility of this medication. Patients are also at risk for the development of blood dyscrasias, and blood tests should be obtained regularly.

Miscellaneous

Magnesium

Research has been performed to evaluate antagonists of the NMDA receptor, including the membrane stabilizing effect of magnesium. A systematic review identified nine RCTs with a total of 418 chronic pain patients, but the marked heterogeneity of these studies (three on NP, three on migraine, two on CRPS type one, and one on cLBP with a neuropathic component) precluded formal meta-analysis. Data were generally mixed or negative, although some individual studies showed significant positive results.[87] Larger-sized and higher-quality RCTs are needed to help determine the role of magnesium in the treatment of chronic NP.

Ketamine

Ketamine, another NMDA receptor antagonist, has been extensively studied for the treatment of NP. Recent studies have suggested that while this medication's analgesic effects are chiefly because of NMDA modulation, other receptors like AMPA may also be involved, as may the metabolite norketamine. Furthermore, ketamine-induced decreases in the sensory-discriminative component of chronic pain tend to not persist beyond the infusion period, suggesting that the ability of ketamine to cause long-term pain relief in some patients may be because of effects on the affective-motivational component of chronic pain.[88] Recently published societal guidelines for intravenous ketamine suggest starting dosing with a single outpatient infusion of at least 80 mg for at least 2 h and assessing patients for response prior to further administrations.[89] There is considerable variability in reported regimens, with some publications describing multiday infusions in intubated patients at doses as high as 7 mg/kg/h.[89] Psychomimetic and cardiovascular side effects are most common, leading some centers to require psychology and cardiology clearances prior to

starting infusions. However, hepatotoxicity (possibly cholestatic in nature) and cystitis have also been reported; the latter is more common with illicit ketamine use. Ketamine should be avoided in patients with active substance use disorders, severe hepatic dysfunction, poorly controlled psychotic disorders, and poorly controlled cardiovascular disease.[89]

Most data for the use of ketamine in chronic pain is related to intravenous administration. A recent meta-analysis aggregated 191 patients from seven studies examining both NP and non-NP pain, finding a significant decrease in pain by NRS compared with placebo up to two weeks post-infusion (mean difference –1.83; 95% CI –2.35 to –1.31; for studies reporting responder rates, the RR for a positive response to ketamine vs. placebo was 2.43, 95% CI 1.10 to 5.40). Subgroup analysis of 79 patients with either NP or mixed neuropathic-nociceptive pain also showed a significant decrease in pain scores following ketamine infusion vs. placebo (mean difference –1.75, 95% CI –2.08 to –1.43).[90] Continued large RCTs are needed to determine ideal intravenous dosing and treatment chronicity. Data are less available and less consistent for oral ketamine, which has only 10%-20% bioavailability.[91,92] The previously mentioned guidelines found low quality evidence for the consideration of oral ketamine (recommended dose 150 mg daily, or 0.5 mg/kg every 6 h) after IV infusions; the risk of abuse with prescribed oral ketamine warrants careful patient selection.[89]

Levetiracetam (Keppra)

Levetiracetam is a newer anti-convulsant that was approved in 1999 as adjunctive therapy for partial seizures in adults. It appears that inhibition of voltage-gated sodium channels or T-type calcium channels is not involved in the anti-convulsant effects of levetiracetam, which does not appear to have direct GABAA receptor effects. The mechanism of action of levetiracetam thus does not involve modulation of the four main systems. The starting dose of levetiracetam is 500 mg twice daily, and it may be increased to a recommended 3000 mg/day in divided doses. Dosages of up to 5000 mg/day have been assessed for the treatment of NP.[93] Its linear pharmacokinetics results in predictable effects as the dosage is increased. Levetiracetam is not metabolized by the cytochrome P-450 system and thus does not have significant drug interactions.[94] Adverse effects include asthenia, dizziness, somnolence, and headache. The drug has several favorable characteristics and has been investigated for adjuvant use in areas such as pain. Unfortunately, in several well conducted RCTs, it was found to be ineffective in the treatment of NP secondary to spinal cord injury,[95] polyneuropathy,[96] and post-mastectomy pain.[97]Meta-analysis of 240 participants with NP in four studies found very low quality evidence and no statistical difference in response to levetiracetam compared with placebo.[98]

Botulinum toxin

Botulinum toxin type A (BOTOX, Dysport, Xeomin) is a neurotoxin that causes muscle relaxation by blocking acetylcholine release at the neuromuscular junction. It is FDA approved to treat urinary incontinence associated with detrusor overactivity associated with a neurologic condition, chronic migraine, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm, and strabismus. It can also be used in the treatment of chronic pain, including neuropathic pain and musculoskeletal pain. The analgesic mechanism of botulinum toxin type A (BTX-A) for neuropathic pain may be related to the inhibition of nociceptive neurotransmitters such as glutamate, CGRP, and substance P, as well as reduction of transient potential vanilloid 1 (TRPV1) channel activity.[99] Side effects can include injection site irritation and pain, muscle weakness, and rash. The FDA has also placed a black box warning because of the potential for delayed distant spread of this neurotoxin beyond the administration site leading to a botulism-like syndrome: swallowing and breathing difficulties, severe muscle weakness, and speech dysfunction.

Data for botulinum toxin in neuropathic pain conditions are primarily available for TN and PHN. A recent meta-analysis including 391 subjects from ten RCTs for TN and peripheral neuropathic pain identified a pooled effect of BTX-A three months after treatment superior to placebo: standardized mean difference –0.55 NRS points, 95% CI –0.87 to –0.22. Subsequent subgroup analysis found that the greatest decrease in pain intensity was seen in TN and PHN patients.[100] Another meta-analysis of 495 patients with undifferentiated neuropathic pain from 12 RCTs also found a significant pain reduction with BTX-A at 24 weeks (mean difference –1.61 NRS points, 95% CI –2.81 to –0.40).[101] A small meta-analysis of BTX-A for PDN has also been published (two studies; 58 patients), showing a pain reduction of 1.96 NRS points (95% CI –3.09 to –0.84) following treatment.[102] Further large high quality RCTs are necessary to determine the role of this medication in the treatment of NP. It may be reasonable to consider BTX-A use for NP patients who are unresponsive to standard therapy.

BTX-A has been studied in chronic musculoskeletal pain conditions, including cLBP and MPS. In a study on cLBP, 15 patients with cLBP received 200 units BTX-A in the lumbar spine paraspinal muscles, and 16 received a normal saline injection.[103] Those who received BTX-A injections had superior pain relief compared to saline injections at three and eight weeks after treatment. Numerous RCTs have been performed investigating BTX-A for chronic MPS. Most investigated patients with cervical and shoulder girdle MPS, and the majority utilized a placebo or control procedure. The sole study looking at lumbar MPS was performed by De Andres et al. and found that BTX-A was not superior in efficacy to placebo but was efficacious in a within-group analysis.[104] Seven studies showed superior efficacy of BTX-A injections for cervical MPS either compared to saline,[105–109] local anesthetic and dry needling,[110] or steroid.[111] Eight published studies had negative findings where BTX-A was not found to have superior efficacy to control procedure, either saline,[112–118] or local anesthetic.[119] The discrepancies between positive and negative studies have been postulated to exist because of heterogenous research design methodology and the use of control procedures that are thought to produce analgesic benefits of their own.[120]

Capsaicin

Capsaicin, the active compound in chili peppers, binds to the TRPV1 nociceptor in the skin, causing depolarization and action potential formation classically felt as a burning or pricking sensation. Its analgesic properties are thought to be because of repeated application (or a single application of highly concentrated capsaicin), causing long-lasting "defunctionalization" marked by reversible degeneration of nerve terminals. The principal adverse effects of capsaicin, unsurprisingly, are stinging, burning, and redness at the application site (these also make placebo-controlled study design challenging). There are also reports of respiratory irritation from inhalation of dried cream. Capsaicin is available in both low (<0.2%) and high dose (8%) formulations. Most studies of the low dose version have not shown results superior to placebo.[121]

The 8% formulation (Qutenza), which requires supervised administration and subsequent monitoring, has been studied in

two recent meta-analyses. For its principal indication, PHN, significantly more subjects receiving capsaicin in four studies with 1272 participants reported a ≥30% reduction in pain at two to eight weeks compared with active placebo (typically 0.04% capsaicin). RR was 1.3 (95% CI 1.1 to 1.5) and NNT 11 (95% CI 6.8 to 26). Data on ≥50% improvement in pain over the same period was available from three studies with 870 participants and similarly showed an RR of 1.4 (95% CI 1.1 to 1.9) and NNT 12 (95% CI 7.2 to 41). Evidence was graded as moderate quality. Very low quality evidence was found for 8% capsaicin use in HIV neuropathy and PDN. For the former, a meta-analysis of two studies with 801 participants showed an RR of 1.4 (95% CI 1.1 to 1.7) and NNT 11 (95% CI 6.2 to 47) in favor of capsaicin. For the latter, a single study of 369 subjects found that PGIC of "much improved" or "very much improved" occurred more frequently at eight weeks after capsaicin administration (RR 1.3 [95% CI 1.0 to 1.8] and NNT 10 [95% CI 5.2 to 520]).[122] A network meta-analysis for PDN that compared 8% capsaicin with several oral neuropathic agents included 25 RCTs and found that ≥30% reduction in pain was significantly more common with capsaicin than placebo (OR 2.28 [95% CI 1.19 to 4.03]). Statistically significant superiority was not seen compared with pregabalin, gabapentin, or duloxetine, although data suggested similar efficacy.[123] Overall, it is reasonable to consider high dose capsaicin therapy for refractory neuropathic pain, particularly PHN and PDN (its two FDA approved indications), keeping in mind the practical considerations necessary for administration.

Low Dose Naltrexone

Naltrexone, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one, is a long-acting opioid receptor antagonist that was initially approved by the FDA in 1984 for the treatment of opioid dependence and is currently also FDA approved for the treatment of alcohol dependence.[124] Naltrexone and its active metabolite, 6-beta-naltrexone, are reversible competitive antagonists at μ-opioid and κ-opioid receptors, with the highest affinity for μ-opioid receptors.[124,125] The standard dose of naltrexone for the FDA approved indications at 50 to 150 mg also prevents inhibition of γ-aminobutyric acid receptor and inhibition of dopamine release. The premise behind using low dose naltrexone (LDN) stems from the fact that its kinetics do not follow a linear dose-effect curve. Rather, it follows multiple dose-dependent pharmacologic pathways with different end results. LDN has been identified to have multiple mechanisms of action that underlie its emerging utility in chronic pain syndromes, including transient opioid receptor blockade, which upregulates opioid signaling, glial modulation with a neuroprotective effect via inhibition of microglial activation in the CNS through Toll-like receptor four antagonism, and blockade of the opioid growth factor (OGF) receptor resulting in biofeedback response that increases production of endogenous OGF, also known as [Met5]-enkephalin, with a concomitant increase in μ-opioid, δ-opioid, and OGF receptor expression, thereby facilitating interactions between OGF and opioid growth factor receptor (OGFr).[124,126,127]

With a therapeutic dosing range of 0.5 to 9 mg taken once daily (most commonly 3-5 mg), LDN has been shown in multiple published case reports and studies to be efficacious in improving chronic pain severity in patients with fibromyalgia,[126,128–130] CRPS,[131] cLBP,[132] and PDN.[133] Naltrexone is an inexpensive medication with a low side effect profile, with some reported incidences of vivid dreams, nightmares, headaches, and anecdotal reports of anxiety and tachycardia. Current evidence supports its safety and tolerability, and most available evidence shows improvement in subjective pain measures such as quality of life and self-reported pain, but objective data are limited.[134] There are currently no guidelines for the clinical use of LDN and no FDA approved use for naltrexone at any dosage to treat chronic pain. In addition, LDN is not commercially available and must be produced in a compounding pharmacy.

To conclude, naltrexone remains an off-label option for the treatment of chronic pain. Further clinical research with RCTs is warranted, and the use of this medication is recommended for those chronic pain patients who fail gold-standard or other conventional therapy.

Conclusion

There exists a wide variety of non-opioid adjuvant medications for the treatment of chronic pain syndromes. The majority of RCTs to determine the effectiveness of these agents have involved select conditions, with extrapolation of these results to other chronic pain conditions based on the known underlying pathophysiology. As the science of pain medicine has advanced, studies have begun to examine less common chronic pain conditions and the efficacy of these adjuvant agents to treat them. Emerging therapies including NMDA antagonists, capsaicin, and LDN show promising results, but large-scale confirmation via well-designed RCTs is lacking.

Key Points

- Multimodal medical management of cancer- and non-cancer-related pain can involve the use of non-opioid medications, as well as opioid medications.
- Calcium channel modulators used to treat chronic pain, such as gabapentin and pregabalin, bind to the $\alpha_2\delta$ subunit of L-type voltage-gated calcium channels and result in decreased release of glutamate, norepinephrine, and substance P.
- Evidence is strongest for gabapentin and pregabalin as the membrane stabilizers that are most efficacious for neuropathic pain and a variety of other chronic pain syndromes.
- Topiramate has not been convincingly shown to be efficacious for the treatment of chronic pain.
- With rare exceptions, benzodiazepines should not be used to treat chronic pain because of their considerable risks and limited evidence of benefit.
- Intravenous lidocaine has shown promising short-term effects for treating chronic pain, but data are lacking for longer-term benefit.
- Intravenous ketamine is quite propitious for chronic pain, but further research is required to determine the optimal dose and treatment chronicity.
- Botulinum toxin type A, high dose topical capsaicin, and LDN may be considered in refractory chronic pain.

Acknowledgments

The authors gratefully recognize the contributions of Dr. Brian E. McGeeney, co-author of the prior edition of this chapter.

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Skeletal Muscle Relaxants

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The term *skeletal muscle relaxant* can be confusing for patients and clinicians alike as there are different classes of skeletal muscle relaxants. Specifically, antispasticity, antispasmodic classes of skeletal muscle relaxants exist, and some medications overlap in both of these categories. (Table 55.1).[1–4] The use of such agents with or without nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered for acute low back pain.[5] Medications commonly referred to as skeletal muscle relaxants include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine.[6] These agents are labeled by the United States Food and Drug Administration (FDA) with an indication for the relief of discomfort associated with an acute, painful, musculoskeletal condition. Baclofen and tizanidine have FDA indications for the treatment of spasticity caused by upper motor neuron syndromes, including multiple sclerosis and spinal cord disease or injury. Benzodiazepines, principally diazepam, are also used and indicated for adjunctive relief of skeletal muscle spasms and are often considered in discussions regarding skeletal muscle relaxants.

In discussing this broad class of skeletal muscle relaxants medications, it becomes difficult to cull out the actual intended therapeutic outcomes. These agents are typically prescribed during the initial presentation of acute low back pain. The injury normally occurs to the muscles, ligaments, or tendons, structures around the lumbar spine. The presentations may include local pain and tenderness, muscle spasms, and limited range of motion. Muscle spasm is often the most difficult to define and is the subject of controversy among some clinicians.[7] Muscle spasm can be described as a vicious pain-spasm-pain cycle that protects compromised tissues and structures. Secondary to these pain impulses, an involuntary reflex muscle contraction at the site of injury can occur, which in turn can lead to local ischemic injury. This can further facilitate the pain-spasm-pain paradigm. Muscle spasm phenomena may be considered a variation of a myofascial pain presentation.[8]

Mechanism of Action

In considering this discussion of muscle spasm pathophysiology, the problem with defining the activity of the skeletal muscle relaxants becomes manifest. The exact mechanism of action for these various agents has not been fully elucidated. However, it is generally accepted that skeletal muscle relaxants can depress polysynaptic reflexes within the dorsal horn via various mechanisms (Box 55.1), which may relax the skeletal muscle tissue in an indirect manner.[1–3] In animal studies, these agents exert their muscle-relaxing effects by inhibiting interneuronal activity and blocking polysynaptic neurons in the spinal cord and descending reticular formation in the brain. Interesting to note is that sedating agents also depress polysynaptic reflexes, making it difficult to determine whether skeletal muscle relaxants produce their clinical activity via sedation or a change in the pain-spasm-pain cycle.

• BOX 55.1 Classification of Agents by Proposed Mechanism of Action

Drug	Mechanism of action	Site of action
Baclofen	Similar to GABA acts on the presynaptic $GABA_a$ site, decreasing synaptic transmission to the spinal cord	Centrally acting-spinal cord
Dantrolene	Prevents the release of calcium from the sarcoplasmic reticulum in skeletal muscle cells	Peripherally acting
Carisoprodol	Causes altered neuronal output at the reticular formation and spinal cord	Centrally acting - spinal cord and brain
Chlorzoxazone	Acts on the spinal cord and subcortical regions to inhibit reflex arcs involved in causing and maintaining muscle spasm	Centrally acting-spinal cord and brain
Cyclobenzaprine	α_2 agonists at descending noradrenergic neurons on the supraspinal area of the brain stem, seratonergic antagonism at $5HT_2$ receptor	Centrally acting - brainstem
Metalaxone	CNS depressant	Centrally acting
Methocarbamol	CNS depressant	Centrally acting
Orphenadrine	Central atropine like structure alleviates muscle spasm	Centrally acting
Diazepam	Benzodiazepine increases GABA mediated presynaptic inhibition at spinal and supraspinal sites	Centrally acting - spinal cord and brain
Tizanidine	α_2 adrenergic agonist, presynaptic inhibition of motor neurons	Centrally acting
Botulinum Toxin	Neurotoxin- blocks the release of acetylcholine at the neuromuscular junction, causing muscle paralysis	Centrally and peripherally acting

Indications for Use

Despite the common use of skeletal muscle relaxants, relatively little data exist to elucidate their role in the treatment of chronic low back pain.[9,10] None of the agents discussed in this chapter have an indication for use in the setting of chronic back pain. In one survey of skeletal muscle relaxant use in the United States, muscle relaxants, although indicated for short term treatment, are most often prescribed on a long term basis.[11] In general, skeletal muscle relaxants, excluding baclofen and tizanidine, maintain FDA labeling as adjuncts for treatment of short term acute low back pain (LBP) and are commonly used to treat muscle spasms and associated pain for periods of one to three weeks as most patients with acute or subacute low back pain improve with time.[5] In this context, it may be difficult to discern the role of these agents, other than the palliative analgesic quality that they may provide for patients. Therefore skeletal muscle relaxant selection depends on an evaluation of adverse effects, contraindications, patient tolerability, and clinical experience. This discussion will also include a brief review of the clinical use of botulinum toxin as a treatment for musculoskeletal pain.

Specific Drugs By Class

Antispasmodic Agents

Carisoprodol (Soma)

Carisoprodol is a Schedule IV substance and is available as a 250 mg or 350 mg tablet and in combination with aspirin (soma compound) and with aspirin and codeine (soma compound with codeine). Carisoprodol dosing should not exceed four doses in a 24 h period (Table 55.1). In addition, it should not be prescribed for longer than three weeks.[12,13] Similar to other muscle relaxants, carisoprodol has additive sedative effects when taken with alcohol or other central nervous system (CNS) depressants. Its most common side effects are drowsiness, dizziness, and headache.[12–14]

Carisoprodol is converted in the liver to meprobamate, a substance with a long half-life of 10 h.[12,13] Meprobamate is well known to produce phenomena that result in physical and psychological dependence.[13–15] After oral ingestion, carisoprodol has a quick onset of action with time to maximum plasma concentration being 1.5 to 1.7 h.[12] Within the United States since 2012, carisoprodol has been listed as a Schedule IV controlled substance by the Controlled Substance Act. Because of the risk of physical and psychological dependence potential, carisoprodol use should be avoided. It should also be cautiously tapered as opposed to immediately discontinued following long-term use.

Chlorzoxazone (Paraflex, Parafon Forte DSC)

Chlorzoxazone is available as 250 and 500 mg tablets, taken up to four times daily. It is a centrally acting muscle relaxant acting primarily at the level of the subcortical regions of the brain and spinal cord.[16,17] It has been suggested that chlorzoxazone may be less effective than the other skeletal muscle relaxants.[9] It does not have any significant drug-drug interactions, but it does have a significant adverse effect profile that includes a rare idiosyncratic hepatocellular reaction. The role of this agent is unclear, considering the potential lack of efficacy and significant toxicity profile.[16,17]

Cyclobenzaprine (Amrix, Flexeril)

Cyclobenzaprine is available as 5 and 10 mg tablets, with recommended dosing of up to three times daily for up to three weeks as longer therapy is not well supported. It is also available in an extended-release form. Cyclobenzaprine is structurally and pharmacologically related to tricyclic anti-depressants. It is a centrally acting serotonin receptor antagonist as well as an α two agonist at descending noradrenergic neurons rather than a CNS depressant skeletal muscle relaxant.[18–20] As with other skeletal muscle relaxants, cyclobenzaprine does not have activity directly on muscle tissue, with animal data suggesting that this agent acts primarily in the brainstem. The net result of this action is a reduction in tonic somatic motor activity.[21] Although no human evidence exists to support this mechanism, the 5 mg dose has yielded similar clinical efficacy with less sedation than the more sedating 10 mg dose.[22] In the future, this may prove to be an important distinction with other CNS depressant agents. In an open-label study of patients with acute neck or LBP associated with muscle spasm who were randomized to be treated for seven days with cyclobenzaprine 5 mg PO three times daily alone or cyclobenzaprine 5 mg PO three times daily in combination with ibuprofen, at doses of 400 mg PO three times daily or 800 mg three times daily, no significant treatment differences were found among these groups.[23]

Cyclobenzaprine shares a similar side effect profile, including prominent anticholinergic effects, as it is structurally related to tricyclic anti-depressants. The most common anticholinergic side effects include drowsiness, dizziness, and dry mouth. Other side effects also include urinary retention, hypotension, and constipation.[23] Use of cyclobenzaprine is contraindicated in the setting of arrhythmias, congestive heart failure, hyperthyroidism, acute glaucoma, narrow angle glaucoma, or during the acute recovery phase of a myocardial infarction. One report suggested that coadministration with pro-serotonergic agents such as selective serotonin reuptake inhibitors may predispose patients to serotonin syndrome.[24]

Cyclobenzaprine can increase the risk of serotonin syndrome in patients taking tramadol, increasing the risk of seizures. Attendant use of cyclobenzaprine with monoamine oxidase inhibitors or use within 14 days after their discontinuation is contraindicated. It can also enhance the effects of agents with CNS depressant activity. Older adults appear to have a higher risk for CNS-related adverse reactions, such as hallucinations and confusion when using cyclobenzaprine. Withdrawal symptoms have been noted with the discontinuation of chronic cyclobenzaprine use. Use of a medication taper may be warranted for chronic-use patients.

Metaxalone (Skelaxin)

Metaxalone is available as a 400 and 800 mg tablet and has a recommended maximal dose of 800 mg three or four times daily. Its exact mechanism of action is not well understood, but it does cause general depression of the CNS.[25] Metaxalone does not have any significant drug-drug interactions and appears to have a minimal risk side effect profile. However, fatalities attributed to the use of metaxalone have been reported.[25,26] Hemolytic anemia, leukopenia, and impaired liver function have been seen with the use of metaxalone, but they are uncommon. Metaxalone is contraindicated in patients who have severe renal or hepatic impairment. It is known to cause an elevation in the cephalin flocculation test, necessitating serial liver function assessments. Metaxalone can also produce a false-positive result for Benedict's test. In this scenario, alternatives to urine glucose testing may be necessary.[27,28]

Methocarbamol (Robaxin, Robaxisal)

Methocarbamol is available in oral and parenteral forms. However, many complications have arisen with the injectable form, including pain, sloughing of the skin, and thrombophlebitis. The exact mechanism of action is unknown. However, it causes general

TABLE 55.1 Skeletal Muscle Relaxant Profiles

Drug	Onset of Action	Duration (h)	Dosing (can be taken as needed or standing)	Side Effects	Important Drug Interactions
Dantrolene Antispacticity agent	>7 days (PO)	Variable (PO) peak plasma concentration in 6 h	25–100 mg PO four times daily	Muscle weakness, phlebitis, respiratory failure, gastrointestinal failure	Chronic therapy can cause hepatic dysfunction. Ace-Inhibitors, paralytics, i.e. Vecuronium
Baclofen Antispasticity agent	Three to four days (PO) 4–6 h (IT) 30 min (IT)	Variable (PO)	5–10 mg PO three times daily	Drowsiness, slurred speech, hypotension, constipation, urinary retention	Anti-depressants (short-term memory loss); additive effects with imipramine
Carisoprodol Antispasmodic	30 min	4–6	250–350 mg PO three times daily	Drowsiness, dizziness, headache	CYP2C19 inhibitors and inducers
Chlorzoxazone Antispasmodic agent	~1 h	3–4	250–750 mg PO four times daily	N/V, headache, drowsiness, dizziness	Additive effects when taken with alcohol or other CNS depressants
Cyclobenzaprine Antispasmodic agent	~1 h	12–24	5–10 mg PO three times daily	Drowsiness, dizziness, dry mouth	Additive effects with barbiturates, alcohol, other CNS depressants; seizures with tramadol and MAOIs; additive effects with TCAs
Metaxalone Antispasmodic agent	1 h	4–6	800 mg PO four times daily	Dizziness, headache, drowsiness, N/V, rash	Additive effects when taken with alcohol or other CNS depressants
Methocarbamol Antispasmodic	30 min (PO)	4–6	750–1500 mg PO four times daily	Dizziness, blurred vision, with drowsiness	Additive effects when taken with alcohol or other CNS depressants
Orphenadrine Antispasmodic	1 h (PO)	4–6	100 mg PO twice daily	Tachycardia, lightheadedness, anxiety	Propoxyphene (confusion, N/V, dry mouth, tremors)
Diazepam Antispasmodic and antispasticity agent	30 min (PO)	Variable, depending on elimination	2–10 mg PO four times daily	Sedation, fatigue, hypotension ataxia, respiratory depression	Potentiation of effects when taken with phenothiazines, opioids, barbiturates, MAOIs
Tizanidine Antispasmodic and antispasticity agent	Two weeks	Variable	2–8 mg PO four times daily	Drowsiness, dry mouth, dizziness, hypotension, increased spasm, or muscle tone	Additive effects with alcohol and other CNS depressants; reduced clearance with oral contraceptives

CNS, Central nervous system; *IT*, intrathecal; *MAOIs*, monoamine oxidase inhibitors; *N/V*, nausea and vomiting; *TCA*, tricyclic anti-depressant.

CNS depression. If combined with benzodiazepines, barbiturates, codeine, or its derivatives, methocarbamol can cause respiratory depression.[29] The injectable form should be used cautiously in patients with known latex hypersensitivity. The oral dosage form of the medication is marketed as a 500 and 750 mg tablet, with a recommended daily dosage range of 4000 to 4500 mg as three or four divided doses daily. For difficult situations, the dose for the first 24 to 48 h can be up to 6 to 8 g/day. Methocarbamol is also combined with aspirin and marketed as Robaxisal. In a randomized, double blinded placebo-controlled trial of naproxen with or without orphenadrine or methocarbamol for acute LBP in the emergency department population, no functional improvement was demonstrated in either group compared to placebo with naproxen.[30]

Orphenadrine Citrate (Norflex, Norgesic, Norgesic Forte)

Orphenadrine is structurally related to diphenhydramine and thus exhibits antihistaminic and anticholinergic properties. Orphenadrine appears to block muscarinic acetylcholine receptors and

N-methyl-D-aspartate receptors in the CNS.[31] Like methocarbamol, orphenadrine is available in a parenteral dosage formulation. However, there have been reports of severe adverse reactions with parenteral use (e.g. anaphylactoid reaction), making this formulation difficult to use. Orphenadrine is available as a 100 mg tablet (Norflex) and in combination with aspirin (Norgesic) and caffeine (Norgesic Forte).

Orphenadrine's anticholinergic actions have been noted to produce significant adverse effects at high dosages such as tachycardia, palpitations, urinary retention, and blurred vision.[32] Given its significant anticholinergic profile, orphenadrine use is contraindicated in patients with underlying neuromuscular junction defects such as myasthenia gravis and Lambert Eaton syndrome.

Antispasticity and Antispasmodic Agents

Diazepam (Valium)

Diazepam is approved for the management of anxiety, acute alcohol withdrawal, skeletal muscle spasm, and convulsive disorders.[33] With respect to muscle relaxation, γ-aminobutyric acid (GABA)-mediated presynaptic inhibition at the spinal level is thought to be the main mechanism of action for diazepam.[34] This medication is a Schedule IV controlled substance with serious adverse effects such as sedation and abuse potential and should not be considered as a first-line muscle relaxant agent.[35] It is important to taper this agent slowly after long-term use to avoid any withdrawal symptoms. Withdrawal symptoms can range from mild headaches and pain to psychosis, hallucinations, seizures, mania, and death from convulsions if high dose chronic treatment is stopped abruptly.[36] Diazepam is available in a wide range of dosages, and each patient should be treated on an individual basis. For example, the recommended dosage range for musculoskeletal pain is 2 to 10 mg orally, administered two to four times daily.[34] There are serious medication interactions in patients taking both benzodiazepines and opioids, increasing the risk of respiratory depression and mortality from respiratory failure.

Tizanidine (Zanaflex)

Tizanidine is a centrally acting α-2 noradrenergic receptor agonist and inhibits excitatory neurotransmitters at the spinal and supraspinal levels. Through its inhibition of neurotransmitter release and the spinal pathways that enhance muscle movement, tizanidine has been found to be effective in reducing muscle spasticity in patients with spinal cord injury.[37] The main adverse effects are sedation, dizziness, hypotension, hepatotoxicity, and dry mouth.[38] Liver function tests should be monitored periodically while on this medication. Currently, tizanidine is FDA approved for the management of spasticity, which may be caused by multiple sclerosis, acquired brain injury, or a spinal cord injury. A meta-analysis that compared tizanidine, baclofen, and diazepam found that they were equally effective in decreasing excessive muscle tone in patients with multiple sclerosis or cerebrovascular lesions, and muscular strength improved in all three treatment groups, but the improvement was greatest with tizanidine.[39] There are published studies on tizanidine's effectiveness in cervical and lumbar spine myofascial pain.[40] A double-blind, multicenter study evaluated 105 patients with acute LBP given tizanidine 4 mg PO three times daily with ibuprofen 400 mg PO three times daily, or ibuprofen 400 mg PO three times daily with placebo. The study results suggested that the tizanidine-ibuprofen combination is more effective for treating moderate or severe acute lower back pain than placebo and ibuprofen alone.[41] Dosing for tizanidine begins at 2 to 4 mg tablets daily, usually given at bedtime, and may gradually be increased to a maximum of 36 mg per day, divided three to four times daily, depending on patient tolerance.[42]

Tizanidine should be used with caution in the setting of renal impairment. Tizanidine clearance decreases by 50% in patients with creatinine clearance lower than 25 mL/min. Therefore it is recommended to start patients with renal insufficiency at 2 mg/day rather than at 4 mg/day for this reason.[43] Liver function tests should be monitored regularly while on this medication, as this medication has been found to cause hepatotoxicity. In addition, coadministration with alcohol increases the maximum concentration by approximately 15%, and concomitant use of oral contraceptives decreases the clearance of tizanidine, which can enhance its sedating effects.

Antispasticity Agents

Baclofen (Lioresal)

Baclofen functions as a $GABA_B$ receptor agonist and produces its effects by inhibiting monosynaptic and polysynaptic transmission along the spinal cord. This drug is FDA approved for the management of reversible spasticity, particularly for the relief of flexor spasms, clonus, and associated pain, which commonly occurs in patients with spinal cord lesions and multiple sclerosis.[44] Studies have shown baclofen to have superior efficacy and tolerance when compared with tizanidine.[45] Baclofen can be administered intrathecally in cases of severe spasticity and for patients who do not tolerate or have failed oral therapy. Intrathecal baclofen therapy allows a patient to receive a high concentration of the medication directly to the spinal cord while reducing the CNS side effects, such as sedation, that develop with high oral doses of baclofen.[46] Oral administration of baclofen is initially 5 mg three times per day with a dose increase every three days until optimal response is achieved. However, the dose should not exceed 80 mg daily. The usual therapeutic range of baclofen is 40 to 80 mg daily.[44] Common adverse effects of baclofen are muscle weakness, somnolence, paresthesia, vertigo, and nausea.[47] A gradual dose reduction is recommended to prevent withdrawal symptoms. Abrupt discontinuation of oral baclofen can cause seizures and hallucinations, while discontinuation of intrathecal baclofen may result in hyperpyrexia, impaired mental status, muscle rigidity, and severe rebound spasticity. As baclofen use can lead to adverse effects in several organ systems, it should be used with caution in older patients and patients with renal impairment.[48]

Dantrolene

Dantrolene is a direct acting skeletal muscle relaxant that interferes with the release of calcium ions from the sarcoplasmic reticulum in skeletal muscle cells. It binds to the ryanodine receptor 1 and decreases intracellular calcium. This, in turn, slows the contraction cycles of muscle cells. It is FDA approved to treat malignant hyperthermia in both adults and children, neuroleptic malignant syndrome, as well as upper motor neuron disorders involving the brain and spinal cord. It is not recommended to be used as an agent for acute musculoskeletal pain.

It is available in both oral and intravenous forms. Common adverse effects include skeletal muscle weakness, hepatotoxicity. Therefore it is contraindicated in patients who have preexisting underlying liver disease.[31,49]

Botulinum Toxins (Botox-onabotulinumtoxin A, Dysport-abobotulinumtoxin A, Xeomin-incobotulinumtoxin A, and Myobloc-rimabotulinumtoxin B)

Botulinum toxin is a potent neurotoxin protein produced by the gram-positive anaerobic bacterium *Clostridium botulinum*.[50] Botulinum toxin types A and B have been developed for routine commercial use. The toxin's primary mechanism of action has been linked to its ability to inhibit the release of acetylcholine from cholinergic nerve terminals. However, it also inhibits the release of glutamate, substance P, and calcitonin gene-related peptide, as well as inhibiting the expression of the transient receptor potential vanilloid type 1 (TRPV1) and Purinergic ($P2X_3$ receptor) in the dorsal root ganglion (DRG) ganglion.[51] These effects likely contribute to the analgesic properties of botulinum toxin. Botulinum toxin has been studied in several chronic pain conditions associated with painful muscle spasms, including head and neck myofascial pain, temporomandibular joint disorders, cervical dystonia syndromes, and chronic LBP.

The potential benefit of botulinum toxin for the treatment of chronic myofascial pain in the head and neck has been noted. A 2016 meta-analysis reviewed 13 randomized controlled trials evaluating the efficacy of botulinum toxin type A injections for head and neck myofascial pain compared to placebo.[52] This review included a total of 656 total participants, with 366 receiving botulinum toxin type A injections to myofascial trigger points and 290 participants in the control group receiving saline injections. This review concluded no significant improvement in pain intensity at four to six weeks posttreatment with botulinum toxin injections. However, there was a significant improvement in pain intensity with botulinum toxin injections at two to six months compared to placebo ($p=0.008$).[52] A 2017 retrospective review evaluated the efficacy of botulinum toxin (onabotulinumtoxin A, Botox) for patients with chronic temporomandibular disorders with injections into the temporalis and masseter muscles. Fifty-five of the 71 subjects (77%) reported beneficial effects with Botox. In addition, patients reported a greater pain improvement after Botox injections at five to ten weeks post-injection compared to less than five weeks ($p=0.009$).[53] This is consistent with the above meta-analysis, showing pain improvement several weeks after botulinum toxin injections. More recently, a randomized clinical trial evaluated onabotulinum toxin A injections for the treatment of masseter and anterior temporalis myofascial pain.[54] This study concluded that botulinum toxin injections reduced pain intensity ($p<0.0001$) and increased pressure pain threshold ($p<0.0001$) for up to 24 weeks compared to placebo. However, dose-related adverse effects were seen, such as a transient decline in masticatory performance ($p<0.05$), muscle contraction ($p<0.0001$), and decrease in muscle thickness ($p<0.05$) and coronoid and condylar process bone volume ($p<0.05$).[54] As a result of these findings, low doses of botulinum toxin are recommended for persistent myofascial pain that does not improve with conservative treatments.

Botulinum toxins are considered first line therapy for the treatment of cervical dystonia, and a systematic review and meta-analysis were published in 2014 evaluating the efficacy of onabotulinumtoxin A in these patients.[55] A total of 18 studies were reviewed in the meta-analysis showing a mean duration of 93.2 days after injections with onabotulinum toxin A and doses greater than 180 units were associated with longer durations of effect (107–109 days) compared to less than 180 units (86–88 days, $p<0.01$).[55] Based on the published literature and duration of effect, patients with cervical dystonia treated with onabotulinumtoxin A should require approximately four treatments annually.

Botulinum toxin injections have also been studied in the treatment of chronic LBP. In one study, 31 patients with chronic LBP were randomized, 15 patients received 200 units of botulinum toxin A (onabotulinumtoxinA) injected into five sites (40 units injected per site at five lumbar paravertebral levels), and 16 patients received placebo injections.[56] Pain and disability were measured at three and eight weeks after injection using both the visual analog scale (VAS) and the Oswestry LBP and disability questionnaire. At three weeks, 73.3% of the patients receiving botulinum toxin A had >50% pain relief vs. 25% of patients receiving placebo ($p=0.012$). At eight weeks, 60% of patients receiving botulinum toxin A and 12.5% of patients receiving placebo injections experienced pain relief ($p=0.009$).[56] None of these patients experienced adverse effects. This study concluded that botulinum toxin A injections within the paravertebral muscles could improve chronic LBP and physical functioning at three and eight weeks posttreatment. An open-label pilot study also evaluated the efficacy of botulinum neurotoxin A on patients with chronic LBP.[57] The effect of botulinum toxin A on chronic LBP was prospectively studied in 75 patients with repeated treatments over the course of 14 months. Injections were placed into the paraspinal muscles at four to five levels between L1 and S1, with dosing ranging between 40 and 50 units per site. Pain intensity using the VAS pain frequency, functional status using the Oswestry scale were assessed at baseline, three weeks, and at two, four, six, eight, ten, 12, and 14 months. At three weeks, 40 patients (53%) and at two months, 39 patients (52%) reported significant pain relief. The change in VAS, Oswestry score, and the number of pain days were significant compared with baseline at two months after each injection period ($p<0.005$) and continued to remain significant over subsequent treatments. The majority, 91%, responded well to the injections throughout the length of the study, with 4% of the patients experiencing transient mild flu-like symptoms.[57]

Conclusion

Clinical data has shown that skeletal muscle relaxants are more effective than placebo in relieving acute LBP.[58] It is important to recognize the different classes of muscle relaxants and the intended effect when selecting an agent for a patient. Most clinical guidelines list skeletal muscle relaxants as optional agents for use individually or in combination with an NSAID. An open-label, prospective, multicenter study evaluated patients with acute LBP and provided either a fixed dose combination of chlorzoxazone 500 mg and ibuprofen 400 mg or ibuprofen 400 mg alone for three times daily for a total of seven days.[59] This study revealed that the fixed dose combination of chlorzoxazone and ibuprofen demonstrated a superior efficacy than ibuprofen monotherapy in acute LBP patients. Most clinicians and researchers agree that skeletal muscle relaxants may be beneficial to patients with acute LBP by reducing the duration of discomfort and accelerating functional recovery. It is recommended to consider the use of skeletal muscle relaxants as an adjunct or alternative to NSAIDs, especially in cases in which NSAID toxicity is a concern or when NSAID monotherapy proves suboptimal.

Skeletal muscle relaxants have CNS depressant effects and should be used with caution, particularly for the elderly and in patients with concomitant use of alcohol, anxiolytics, opioid analgesics, and/or other sedating medications. Skeletal muscle relaxants are associated with higher risks for total adverse effects, especially those involving the CNS. The most common and

consistent adverse effects noted with the CNS were drowsiness and dizziness.[60] The benzodiazepines-muscle relaxants such as diazepam and sedative-muscle relaxants such as carisoprodol are highly addictive and should never be used as first line agents.[61]

Considering many medications are found to be ineffective or not tolerable by some patients (e.g. adverse effects of NSAIDs), it is important to consider the use of skeletal muscle relaxants in patients with persistent and intractable myofascial pain.

Key Points

- There are three broad classes of muscle relaxants: antispasmodic, antispasticity, and combination agents.
- Muscle relaxants may treat muscle spasticity in two manners. First, they can modify the stretch reflex arc, either by reducing the excitatory signals or by augmenting the inhibitory interneurons. This decreases activation of the alpha motor neuron. Second, they can disrupt the excitation-contraction coupling that produces muscle contraction.
- Cyclobenzaprine is a centrally acting skeletal muscle relaxant that is structurally related to tricyclic anti-depressants; it acts primarily at the level of the brainstem.
- As a $GABA_B$ agonist, baclofen causes hyperpolarization and thus decreases the release of excitatory neurotransmitters in the brain and spinal cord. It causes less sedation than benzodiazepines and may reduce pain by decreasing substance P release.
- Skeletal muscle relaxants have been shown to be more effective than placebo for patients with acute LBP with respect to outcomes, such as short term pain relief, global efficacy, and improvement of physical outcomes.
- Botulinum toxin not only inhibits the release of acetylcholine from cholinergic nerve terminals but has also been found to inhibit the release of glutamate, substance P, and calcitonin gene-related peptide, as well as inhibiting the expression of the transient receptor potential vanilloid type 1 (TRPV1) and $P2X_3$ receptors in the DRG ganglion. These effects contribute to its analgesic properties.
- Botulinum toxin type A (onabotulinumtoxinA) injections are found to be effective for head and neck myofascial pain, temporomandibular joint disorders, cervical dystonia, and chronic LBP.
- Carisoprodol is converted in the liver to meprobamate, an intravenous controlled substance. Meprobamate is well known to produce phenomena that result in physical and psychological dependence.

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Cannabinoids for Pain Management

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Introduction

Cannabis is a plant genus in the family of Cannabacae, and its medical use dates to ancient China (around 2,700 BC).[1] Its use for medical purposes was first recorded in the worlds' oldest pharmacopeia, the Pen-Ts'ao Ching. Cannabis was indicated for diseases such as rheumatic pain, intestinal constipation, and others.[1] Though awareness about its medicinal properties spread soon to India, Middle East, Africa, Europe, and the Americas, it was not until the 18th century when Willian B. O'Shaughnessy, an Irish physician, first introduced cannabis and its use for rheumatism, convulsions, and muscular spasms in the Western medicine.[2] Cannabinoids have the potential to treat several medical conditions, including refractory epilepsy, cancer chemotherapy induced nausea and vomiting (CINV), and loss of appetite and weight loss in people with HIV/AIDS. In addition, there is a growing body of evidence for the analgesic effect of cannabinoids for acute and chronic pain.[3–5] Cannabinoids also are a potential option to reduce the dose of opioids prescribed for chronic pain.[6] Today, cannabis and its related products have gained a broader acceptance in the popular culture with widespread recreational and medicinal use.

Definitions/Terminology

The cannabis genus encompasses many species, but the most well-known are *cannabis sativa, cannabis indica,* and *cannabis ruderalis*. The cannabis plant contains about 540 chemical substances, and the word "cannabis" refers to all products derived from the plant *cannabis sativa*. The word "marijuana" refers to parts of or products from the plant *cannabis sativa* that contain substantial amounts of Δ9-tetrahydrocannabinol (THC), the substance primarily responsible for cannabis's physiologic effects through its actions on cannabinoid receptors (CBR).[7] The term "medical marijuana" refers to using the whole, unprocessed marijuana plant or its basic extracts to treat medical conditions.[8]

Cannabinoids are a group of over 100 different chemicals found in the cannabis plant that are used for recreational or medicinal purposes. In addition to THC, cannabidiol (CBD) and cannabinol (CBN) are other cannabinoids found in cannabis that stimulate CBR. The cannabis plants also contain over 120 volatile compounds that are called terpenes and sesquiterpenes that are responsible for their characteristic aroma. Synthetic cannabinoids are products manufactured to stimulate CBR.[9]

Endocannabinoid System

The endocannabinoid system is a complex biologic system composed of endogenous CBR and their respective agonists. It is involved in the regulation of multiple physiologic and cognitive processes in the human body to maintain homeostasis.

Cannabinoid Receptor

CBR are cell membrane G protein-coupled receptors (GPCR) with seven transmembrane spanning domains.[10] These receptors are of two types, cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R), and these were identified and cloned in 1990[11] and 1993.[11,12] CBR exist in various locations in the body such as the brain, spinal cord, pituitary gland, thyroid gland, adrenal gland, and digestive system,[13–16] but their distribution, signaling pathways, and functions are still being elucidated.[17–19] Please see Table 56.1 for details.

The GPCR 18, 55, and 119 (GPR18, GPR55, GPR119)[20] are novel CBR that can be activated by several ligands, including THC, arachidonoylethanolamine (anandamide or AEA), and 2-Arachidonoylglycerol (2-AG) and many other non-cannabinoid compounds such as lysophosphatidylinositol (LPI).[21] GPR18 is involved in microglia migration.[22]

Molecular and Cellular Consequences of Cannabinoid Receptor Activation

A variety of cellular functions, including synaptic transmission, gene transcription, and cell motility, are modulated by CB1R and CB2R.[23] CB1R mediates the function of both excitatory and inhibitory neurotransmitters (acetylcholine, noradrenaline, dopamine, serotonin, GABA, glutamate, D-aspartate) and cholecystokinin.[23] Both CB1R and CB2R inhibit the activity of cAMP, decrease cAMP production, and increase the activity of mitogen-activated protein kinases.[10] Activation of CB1R stimulates inwardly rectifying potassium channels and inhibits L-, N- and P/Q-type voltage-activated calcium channels, thus decreasing neurotransmitter release.[24] CB2R shares a similar signaling pathway as that for CB1R but with different affinities and minimal effect on ion channels.[10] A subpopulation of CBR is also detected intracellularly in the lysosome, endosome, and mitochondria. They have distinct pharmacologic properties, including inhibition of

TABLE 56.1 Cannabinoid Receptors and Their Roles

	CB1R	CB2R
Location	Predominantly in the central nervous system (CNS: brain - hippocampus, basal ganglia, cerebellum, olfactory bulb, amygdala, hypothalamus, and cerebral cortex,[14] spinal cord, dorsal root ganglion); some in the peripheral nervous system (PNS), liver, reproductive system, cardiovascular system, and gastrointestinal system	Predominantly in the peripheral tissues, immune cells, hematopoietic cells, bone, liver, keratinocytes, PNS, and some in the CNS[15]
Chromosome location of cannabinoid receptor gene	Chromosome 6	Chromosome 1
Physiologic actions	Psychoactivity, pain & memory processing, and motor control[16]	Regulation of analgesia in response to inflammation, peripheral analgesia, intestinal inflammatory response, and neuroimmune interactions[17]
Involvement in disease processes	Anxiety, depression, addiction, schizophrenia, stroke, multiple sclerosis, neurodegeneration, and epilepsy[18]	Alzheimer's, multiple sclerosis, autoimmune diseases, hepatitis, endometritis, pancreatitis, and inflammatory bowel disease[19]

mitochondrial cellular respiration and cAMP production, hence regulating cellular energy metabolism.[10,25]

Endocannabinoids

Endocannabinoids are endogenous fatty acid neurotransmitters that are responsible for intercellular signaling. Seven endocannabinoids have been identified to date, but the most studied are AEA and 2-AG.[26] AEA is a high-affinity, partial agonist for CB1R, with very-low efficacy at CB2R, whereas 2-AG is a full agonist at both CB1R and CB2R with moderate-to-low affinity.[27] Endocannabinoids' concomitantly interact with other receptors involved in pain, such as transient receptor potential cation channel vanilloid 1 (TRPV1) and peroxisome proliferator-activated receptors. These interactions may contribute to their regulatory role in synaptic transmission and analgesic effects.[28] Endocannabinoids are produced as part of a specific physiologic response against tissue injury in neuronal and non-neuronal cells. They participate in pain inhibition, sensitization, and modulation of the inflammatory response through CB1R and CB2R signaling described above.[28] Both anandamide and 2-AG are autocrine and paracrine messengers. They act through retrograde signaling for synaptic transmission. Endocannabinoids are produced on-demand from post-synaptic vesicles in response to increased intracellular calcium concentration from membrane lipid precursors, and unlike traditional neurotransmitters, they are not produced and accumulated intracellularly.[29] AEA and 2-AG have a short duration of action. They are degraded efficiently by enzymatic degradation, hydrolysis, or oxidation, respectively, by fatty acid amide hydrolase (FAAH) on AEA and monoacylglycerol lipase on 2-AG.[29,30]

Cannabinoid

Phytocannabinoids

Phytocannabinoids are natural substances capable of either directly interacting with CBR or sharing chemical similarities with endocannabinoids or both. More than 100 active phytocannabinoids have been identified within the *cannabis Sativa* plant alone.[31] Cannabinoids, including cannabis terpenoids, have also been identified in other plant species.[32] Besides phytocannabinoids, cannabis sativa, contains additional pharmacologically active molecules, such as terpenoid and β-caryophyllene, that are members of other chemical families. These also interact and mediate potential therapeutic actions through CBR.[7]

The two most studied phytocannabinoids, CBD and THC, were discovered in 1940 and 1964, respectively. THC acts as a partial agonist at CB1R and CB2R,[33] and it is the primary psychoactive component of cannabis. In animal studies, activation of CB1R by THC suppresses locomotor activity and is associated with hypothermia and antinociception in the tail-flick or hot-plate test.[34] THC also has other effects, including stimulating appetite, antiemesis, antispasticity, and analgesia. CBD is a non-psychoactive phytocannabinoid, and it accounts for 40% of the *cannabis Sativa* extract.[35] It acts as a partial antagonist of CB1R (i.e. it attaches to the active site but does not completely block out CB1R's effects) and as a weak inverse agonist of CB2R (i.e. it indices a pharmacologic response opposite to that of an agonist).[36,37] CBD also interacts with other non-cannabinoid targets, including the 5-HT1A receptor, TRPV1, and adenosine A2A receptors that regulate the perception of pain.[38] CBD can act as a non-competitive negative allosteric modulator of CB1R and,[39] in the presence of THC, CBD has complex physiologic effects. CBD works synergistically with THC for its analgesic effect while decreasing THC's psychoactive and cognitive side-effects such as sedation and memory impairment.[40]

In addition, various extracts of cannabis are offered to consumers and marketed under miscellaneous categories such as dietary supplements, hemp oil, CBD-enriched products.[7] Popular ingredients added or contained in CBD and hemp oil products include a diverse span of phytocannabinoids ranging from *C. Sativa, b-Caryophyllene, limonene, and cannabichromene*.[7] Given the large assortment of products, Van Dolah et al. have proposed a checklist of four questions to choose high quality products.[7]

1. Does it meet the following quality standards? a. Current Good Manufacturing Practices certification from the United States Food and Drug Administration; b. European Union, Australian,

or Canadian Food Inspection Agency organic certification; c. National Science Foundation International certification
2. Does the company have an independent adverse event reporting program?
3. Is the product certified organic or eco farmed?
4. Have their products been laboratory tested by batch to confirm THC levels <0.3% and no pesticides or heavy metals?

Synthetic Cannabinoids

Synthetic cannabinoids are chemical molecules that have been designed to possess active pharmacologic properties through activation of CBR. Only two synthetic THC have established clinical applications: nabilone and dronabinol. Nabilone is approved for treating CINV, and dronabinol is indicated for the treatment of AIDS-induced anorexia and CINV. The classification of synthetic cannabinoids is according to their chemical families.[9] There is also a separate category of cannabinoid receptor antagonists or inverse agonists that is under research and development.

Classification of Synthetic Cannabinoids

1. Classical cannabinoids: These are the first chemical family developed based on a similar chemical structure as THC and tricyclic dibenzopyran ring.[41]
2. Non-classical cannabinoids: These are the first chemical compounds consisting of cyclohexyl phenol derivatives that were used recreationally as a drug of abuse.[34]
3. Hybrid cannabinoids: These compounds have a chemical structure combining classical and non-classical cannabinoids.[9]
4. Aminoalkylinodoles: This is a large class of chemical compounds structurally dissimilar to THC or endocannabinoid with cannabinomimetic properties.[9]
5. Endocannabinoid analogs or eicosanoid: This is a new group of synthetic cannabinoid discovered in 2012 based on indole-3-carboxylates.[42]
6. Miscellaneous: These are all other compounds not belonging to any of the above families.[9]

Nabilone (Cesamet®)[43]

Nabilone is an oral synthetic THC analog that is available on prescription.[43] It is approved and licensed for the treatment of CINV and AIDS-induced anorexia in many countries. It exerts a complex pharmacologic effect through interaction with CB1R, CB2R, and the endocannabinoid system. Its application in chronic pain has been studied in several small randomized controlled trials (RCTs) on patients with neuropathic pain, fibromyalgia, cancer pain, and chronic non-cancer pain. A recent systematic review by Tsang et al. analyzed current evidence for its role, including eight RCTs, two prospective cohort studies, and one retrospective chart review[44] with the conclusion that nabilone has a role as an adjunct to conventional analgesic pharmacotherapy. In another systematic review and meta-analysis, a subgroup analysis of three RCTs on nabilone, the authors were unable to find support for analgesic efficacy with nabilone in chronic pain.[3] In a more recent systematic review, a subgroup analysis of four RCTs on nabilone demonstrated a small and clinically insignificant VAS reduction of 10%, but the benefit persisted at six months.[5]

Dronabinol (Marinol® and Namisol®)[45,46]

Dronabinol is a synthetic oral THC analog. Similar to Nabilone, it is approved and licensed for the treatment of CINV and AIDS-induced anorexia.[45] There is limited evidence concerning the role of dronabinol and its analgesic efficacy in patients with chronic pain. In a systematic review and meta-analysis that included a subgroup analysis of studies on dronabinol in patients with functional chest pain, multiple sclerosis (with spasticity and central neuropathic pain), amyotrophic lateral sclerosis, idiopathic cervical dystonia, and spinal cord injury, a lack of analgesic benefit with dronabinol was reported following two weeks to six months of use.[5] Namisol® is a novel formulation of natural THC as a tablet.[46] However, there is a lack of data on its efficacy in patients with chronic pain. In a Phase II placebo-controlled study, Namisol failed to demonstrate analgesic efficacy in patients with chronic abdominal pain.[47]

Nabiximol (Sativex®)[48]

Nabiximol is a cannabinoid oromucosal spray containing extract of THC and CBD in a 50:50 ratio, with each spray containing 2.7 mg THC and 2.5 mg of CBD.[48] It is approved for the treatment of spasticity related to multiple sclerosis in many countries. In a subgroup analysis of six RCTs on nabiximol in a systematic review and meta-analysis on cannabinoids for neuropathic pain, the analgesic benefit was found to be uncertain.[3] The difference in the mean pain scores between nabiximol and comparator groups was statistically significant but clinically small in patients with neuropathic pain (mean difference -0.50 points on a 0-10 scale; 95% CI, -0.89 to -0.12 points).[3]

A summary of the pharmacokinetics and applied pharmacology of synthetic cannabinoids is provided in Tables 56.2 and 56.3.

Mechanisms of Analgesia of Cannabinoids

Several analgesic mechanisms have been proposed for cannabinoids' analgesic effect on acute, chronic inflammatory, and neuropathic pain. Similar to opioids, cannabinoids act on both the CNS and the PNS. CBR are involved in the transduction, transmission, modulation, and perception of pain in both the ascending and descending nociception pathways.[49] A summary of these antinociception mechanisms is detailed below.

Acute pain models: Animal studies have demonstrated that intracerebroventricular administration of cannabinoids increased rats' tail-flick latency, thereby suggesting an analgesic effect.[44] In other acute pain models, micro-injection studies of exogenous cannabinoid receptor agonists into the periaqueductal gray (PAG) and the rostroventral medulla (RVM) (both areas responsible for modulation of descending inhibitory pathways), the amygdala and dorsal raphe nucleus resulted in antinociception.[50] Furthermore, activation of the endocannabinoid system inhibits presynaptic neurotransmitter release from GABAergic and glutamatergic neurons through retrograde signaling in the RVM and PAG,[51] and cannabinoids also modulate post-synaptic neuron excitability. Research in the spinal mechanisms of analgesia of cannabinoids demonstrates that intrathecal administration of exogenous cannabinoid agonists attenuates formalin-induced pain behavior in the mouse model.[52] Exogenous cannabinoids also reverse established mechanical hyperalgesia in the partial sciatic nerve ligation model of neuropathic pain via CB1R signaling, and they may be more effective than opioids.[53] In addition, CB1R is abundantly expressed in the PNS, in specific regions such as the primary afferent neurons of the dermis, dorsal root ganglion, and trigeminal ganglion, where it regulates nociception.[54,55] Evidence of peripheral analgesia mechanisms of endogenous CB1R agonists (AEA) and CB2R selective activation in nerve endings in the PNS further supports the role of peripheral

TABLE 56.2 Pharmacokinetics of Synthetic Prescribed Cannabinoids

	Nabilone /Cesamet®[43]	Dronabinol /Marinol®[45,123]	Nabiximol /Sativex®[48]	Cannabidiol /Epidiolex®[124]
Compound	Synthetic THC	Synthetic THC	50:50 THC:CBD extract	CBD extract
Route	PO tablet	PO tablet	Buccal spray	PO solution
Absorption	Rapid and complete	Almost completely absorbed	Rapid	Rapid
Volume of distribution	12.5 L/kg extensive and rapid distribution	~ 10 L/kg extensive and rapid distribution	Extensive	Extensive, 20963 L to 42849 L
Metabolism	Liver - multiple pathways: enzymatic oxidation and reduction	Liver - not well understood: hydroxylation	Liver	Liver and the gut
Excretion	Feces: ~60%; Urine: ~24%	Feces: 50%; Urine: ~15%	Feces Urine	Feces; with minor renal clearance
Elimination half-life	Parent drug: ~2 h Metabolites: ~35 h	Parent drug: ~4 h Metabolites: 25-36 h	THC: ~2 h CBD: ~5 h for two sprays, terminal half-life 24–36 h	56–61 h

CBD, Cannabidiol; *PO*, per oral; *THC*, delta-9-tetrahydrocannabinol.

TABLE 56.3 Applied Pharmacology of Synthetic Prescribed Cannabinoids

	Nabilone/ Cesamet®[43]	Dronabinol/ Marinol®[45,123]	Nabiximol/Sativex®[48]	Cannabidiol/Epidiolex®[124]
Indication	CINV	CINV, AIDS-induced anorexia	Multiple sclerosis induced spasticity	Seizures (Lennox-Gastaut syndrome and Dravet syndrome)
Minimum recommended age	18 years	18 years	18 years	Two years
Dosage formulations	0.25, 0.5 and 1 mg	2.5 mg, 5 mg, 10 mg	10 mL vial - 90 sprays/ vial, vial concentration: THC 27 mg/mL / CBD 25 mg/mL	Oral solution: 100 mg/mL
Dose range	1 or 2 mg BID	2.5 mg orally twice daily	Starting dosage one spray BID, therapeutic: 4-8 sprays daily	Starting dose: 2.5 mg/kg BID, maintenance dose: 5 mg/kg BID, maximum: 10 mg/kg BID
Maximum recommended dosage per day	6 mg	50 mg	12 sprays	20 mg/kg
Adverse effects and other important facts	Nabilone is not detected in drug urine tests	Hypersensitivity reactions to dronabinol or sesame oil	Glossodynia, mouth ulceration, oral discomfort secondary to a reaction to ethanol pain, application site irritation	Possible dose-related elevation of liver transaminases, hypersensitivity to cannabis, require dosage adjustment in hepatic impairment

AIDS, Acquired immunodeficiency syndrome; *CINV*, chemotherapy induced nausea and vomiting.

mechanisms of action for cannabinoids.[54,56] Non-cannabinoids such as meptazinol (a non-opioid analgesic) also display agonism at CBR as one of their analgesic mechanisms,[57] and injection of a CB1R antagonist into supraspinal sites such as the PAG or RVM reverses meptazinol-induced analgesia.[57]

Inflammatory pain models: There is growing evidence for the role of cannabinoids in relieving inflammatory pain. Microinjection studies of exogenous CB1R agonists into supraspinal location inhibits formalin-evoked nociceptive and aversive, panic-like behavior in rats.[58] At the level of the spinal cord, CB2R has been suggested to be involved in rat models of inflammation. CB2R mRNA is upregulated in rats with chronic inflammatory conditions,[59] and CB2R activation influences the CNS response to inflammation through microglial migration.[60] Peripherally, CB2R activation mediates suppression of thermal and mechanical hypersensitivity in inflammatory pain models.[61] Activation of CB2R results in similar anti-allodynic effects in capsaicin models of inflammatory pain.[62]

Neuropathic pain models: Cannabinoid and endocannabinoid interactions provide potential targets for attenuation of neuronal hyperexcitability in the treatment of neuropathic pain. In the neuropathic disease rat model, upregulation of CB1R mRNA in the thalamus, an area of the brain involved in processing pain, has been reported.[63] Multiple experimental animal models based on sciatic nerve injury or ligation (SNI or SNL), spinal nerve ligation, and spared-nerve injury (SPNI) have been used to explore the cannabinoid system's role in neuropathic pain. Studies reported the blockade of TRPV1 and FAAH resulting in decreased symptoms and sequelae in the medial prefrontal cortex of neuropathic pain in the SNI rats model.[64] At the spinal cord level, there is some evidence for synthetic cannabinoids in mitigating mechanical and thermal hyperalgesia or cold allodynia in neuropathic models.[63,65] In summary, *in vitro* and *in vivo* animal studies demonstrate the analgesic potential of cannabinoids. However, more work is necessary for the translation from basic science studies to clinical practice.

Review of Evidence for Cannabinoids' Use in Relieving Chronic Pain

Several studies have evaluated the analgesic efficacy of cannabinoids. A recent systematic review and meta-analysis of 36 RCTs with 4,006 participants by Johal and colleagues examined the evidence for smoked cannabis (four RCTs), oromucosal cannabis sprays (14 RCTs), and oral cannabinoids (18 RCTs).[5] There was a significant but small analgesic effect favoring the use of cannabinoids over placebo (VAS (range 0–10) -0.63, 95% confidence interval [CI]: -0.85 to -0.42), and the evidence was deemed to be of a low quality. Oral cannabis demonstrated a greater reduction in pain than oromucosal and inhaled formulations. Across all routes and formulations, cannabinoids had a greater analgesic effect at two weeks (VAS -0.54, 95% CI: -0.76 to -0.31; moderate quality evidence) as compared to six months (VAS -0.43, 95% CI: -0.75 to -0.10; low quality evidence).[5]

Another systematic review and meta-analysis in 2018 reviewed 104 studies (n = 9,958 participants) with 47 RCTs and 57 observational studies on cannabinoids and analgesia from 1980–2017.[4] Forty-eight studies were on patients with neuropathic pain; seven studies were on fibromyalgia, one was on rheumatoid arthritis, and 48 other were on chronic non-cancer pain. Across RCTs, the pooled event rates (PERs) for 30% reduction in pain scores was significant for cannabinoids (29.0% cannabinoids vs. 25.9% placebo; CI: 15-61%).[4] The review also suggested positive secondary pain-related outcomes with cannabinoids, including low quality evidence for improved sleep and patients' global impression of change.[4] Another systematic review and meta-analysis published in 2017 evaluated cannabinoid analgesic efficacy specifically in neuropathic pain patients, including 11 RCTs (1,219 patients).[3] It reported a statistically significant but clinically uncertain reduction in mean numeric rating scale pain scores (zero to ten scale) compared with comparator groups (-0.65 points; 95% CI: -1.06 to -0.23 points). It also reported secondary benefits with cannabinoids on improvement in quality of life (five out of eight studies) and sleep (six out of seven studies).[3]

Routes of Administration

A large diversity of cannabis-derived products exist in the market for recreational and medicinal uses. The iconic embodiment of consuming cannabis has been linked to inhalation. Inhalation or smoking via a joint, spliff, pipe, blunt, water-pipe/bong is the most commonly used form of consumption.[66,67] Other routes of administrations (ROA) include vaporizing (inhalation), dabbing, e-cigarettes, oral sprays, edibles, drinkables, tinctures (alcohol-based liquid cannabis extracts), other oromucosal/sublingual (e.g. strips and lozenges), transdermal topicals (cannabis-infused lotions, balms, oils), intravenous (syringe), and rectal (suppositories).[68–70]

Both THC and CBD are metabolized extensively in the liver. THC is metabolized via by microsomal hydroxylation and oxidation by cytochrome P450 enzymes CYP 2C9, 2C19, and 3A4,[38] and it is eliminated in the urine and feces. CBD undergoes extensive phase 1 metabolism,[71] and it is metabolized by primary oxidation and side-chain oxidation.[72]

Smoking cannabis results in rapid and efficient absorption with a peak effect, shorter duration of action, and higher blood concentration of THC as compared to other routes (Table 56.4).[73,74,75] Absorption and bioavailability of smoked cannabis depend on the depth of inhalation, type of smoking device, duration of puffs and breath holding, and the composition of cigarettes.[76] Little clinical data exists in the literature for the pharmacology of smoked CBD. It is estimated to be similar to those of THC, including a bioavailability of 31% (range 11%–45%).[77] On average, each joint of cannabis contains 500 mg to 1 g of the cannabis plant, 7.5–225 mg of THC (1%–30%), and 0–180 mg of CBD (0%–24%).[78] Vaporization offers a potentially lower-risk tool with a similar pharmacologic profile as smoked cannabis[79] because it reduces the formation of harmful substances such as carbon monoxide, polycyclic aromatic hydrocarbons, and tar.[79] Variability in the effects of vaporized

TABLE 56.4 Applied Pharmacology of Cannabis-Based Products According to the Route of Administration

	Inhalation[66,67,73–75]	Oral[80,81]	Topical[85]	Liquid Extract[71]	Rectal[84]	Ophthalmic[125]
Absorption	Rapid (seconds)	1–2 h	Variable (enhanced by water and oleic acid in ethanol)	10–45 min	Variable (depends on its base formulation)	1 h
Peak plasma availability	3–10 min	4–6 h	Variable (~1.4 h)	Variable	2–8 h	Several hours
Bioavailability	10%–35%	Variable (6%–10%)	Variable	Variable	Variable (up to 13.5%)	6%–40%
Duration of action	1–6 h	4–12 h	48 h (steady-state)	2–8 h	Variable	Variable

cannabis depends on the type of cannabis, amount of cannabis placed in vaporizer, temperature, and duration of vaporization, and type of vaporizer used. As an example, one single oro-mucosal administration of Nabiximols with four sprays (total of 10.8 mg THC and 10 mg CBD) results in peak plasma concentrations of both THC and CBD within 2–4 h.[48]

In comparison to inhaled routes, oral absorption of cannabinoids is slow, variable, and highly dependable on the associated food ingested with cannabinoids.[80,81] Based on the bioavailability alone, the conversion factor for inhaled to orally ingested cannabinoids has been estimated to be 2.5.[82] Given that cannabinoids are lipophilic, there is weak evidence that fatty meals or a lipophilic formulation (cookie or oil-based) enhance cannabinoid absorption and bioavailability.[83] Any cannabinoid ingested orally undergoes extensive first-pass metabolism in the liver (e.g. dronabinol has a bioavailability of 10%–20% of the administered dose after ingestion).[45,74] However, both rectal and transdermal application of cannabinoids avoid the first-pass metabolism. In rectal suppositories, THC-hemisuccinate formulation can offer a bioavailability of up to 13.5%,[84] and for transdermal cannabis-based products, absorption is enhanced by using water and oleic acid in propylene glycol and ethanol.[85]

Direct data comparing analgesic efficacy and safety profile associated with different ROA of cannabis products is scarce.[68] Large-scale studies have documented the many harmful effects of smoking cannabis.[86] Smoking, as the specific ROA, has been associated with many pulmonary complications listed in the "Acute and Chronic Adverse Reactions" section below. Table 56.4 summarizes important pharmacologic facts related to the ROA of cannabinoids.

Adverse Effects of Cannabinoids With Acute and Chronic Use

Short-term Use

Short-term use of cannabis results in cardiovascular AE manifesting shortly after its use and include tachycardia, supine hypertension, peripheral vasodilation, and orthostatic hypotension.[87–89] A retrospective study reported that the first hour after smoking marijuana is associated with a 4.8 (95% CI: 2.4–9.5) times increase in the risk of myocardial infarction.[88] In the respiratory system, cannabinoids cause bronchodilation and a decrease in airway resistance, but an increase in airway reactivity can also occur.[90] In the CNS, cannabinoid consumption can generate both increased or decreased anxiety and paranoia.[90] Other significant cognitive effects include euphoria, hallucinations, memory impairment, headaches, and dizziness.[87] Inhalation of marijuana is also associated with documented strokes and transient ischemic events.[91,92,93] Though cannabinoids have an appetite-simulating and anti-nausea effects, a cannabinoid hyperemesis syndrome with recurrent episodes of severe nausea, vomiting, and abdominal pain has also been described.[94]

Chronic Use

In chronic cannabinoid users, there is an increase in the annual risk of MI, myocardial infarction from 1.5%–3% per year.[95] In a cohort study in cannabinoid users who sustained a MI, a 4.2 fold increased risk (95% CI, 1.2–14.3) of mortality was also noted.[96] In the respiratory system, the route of ingestion determines the degree of potential harm. For example, chronic smoking of marijuana is associated with chronic cough, bronchitis, and emphysema, similar to cigarette smoking.[87] Chronic users of cannabinoids are also at risk for developing tolerance, addiction, and cannabis use disorder.[90] Three recent systematic reviews and meta-analyses on cannabinoids have reported a large number of AEs with cannabinoids. Non-serious treatment-related AEs include dizziness (most common, seen in 1 in 3 patients), throat discomfort, asthenia, fatigue, drowsiness, dry mouth, increased appetite, hallucinations, nausea, and refractory spasticity.[3–5] Serious AE, requiring either medical intervention or withdrawal from the study have an incidence of 5.9%.[5] Another systematic review for chronic non-cancer pain by Stockings et al. found that PERs for all-cause AEs were 81.2% (cannabinoids) vs. 66.2% (placebo).[4] The number needed to harm (NNH) for nervous and psychiatric-related AEs were three and six, respectively.[4] Given the high prevalence of non-serious AEs and considering the relatively low NNT for cannabinoids, the therapeutic index for these substances seems to be narrow.

Contraindications to the Use of Cannabinoids

Cannabinoids are an emerging pharmacotherapy, and the contraindications to their use are evolving as research continues in this field. The use of cannabinoids is not recommended in patients with a known or suspected hypersensitivity to these compounds.[97] Other absolute contraindications include a personal history of schizophrenia and other forms of psychotic disorders.[98] Cannabinoids are also contraindicated during pregnancy and breastfeeding. In animal models, cannabinoids cause a delay in fetal growth and development and sexual maturation, neurobehavioral changes, and adverse effects on male reproductive organ development and fertility.[99] In the human fetus, cannabinoids may cause severe neurologic impairment in the embryo.[100] Synthetic cannabinoid medications (e.g. Nabilone) are classified in the pregnancy category C evidence of AE on the fetus in animal reproduction studies with no adequate and well-controlled studies in humans. However, potential benefits may warrant the use of the drug in pregnant women despite potential risks.[101] Their use is discouraged during breastfeeding. Evidence of the transfer of cannabinoids through breastfeeding is inconsistent and scarce in the literature. Obstetric and gynecology societies have advised against the use of cannabis-based products during breastfeeding for fear of adverse reactions in infants.[102]

Adult populations with severe cardiovascular, respiratory, liver, or renal diseases require specific medical attention to evaluate the risk-benefit ratio with the use of cannabinoids.[103] In patients on opioids and benzodiazepine, caution should be exercised if cannabinoids are used because of the potential increased risk of sedation and cognitive impairment.[97]

Cannabis-based products are contraindicated in children and adolescents for the treatment of chronic pain with some exceptional medical circumstances.[97] Longitudinal studies about heavy recreational use in young adolescents have reported correlations of cannabinoid use with poor cognitive, psychiatric, and neurodevelopmental parameters.[104] There is a consensus around avoiding the use of cannabinoids in individuals under 25 years old because of ongoing neurologic development.[105] A systematic review in 2017 demonstrated insufficient evidence for medical cannabinoids for neuropathic pain in children and adolescents.[106] Caution should also be exercised in patients with a personal or family history of addiction and mental health disorders. Problematic cannabis use can be associated with a cannabis use disorder based on criteria

in the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition).[107] Clinical tools have been developed to screen rapidly for the severity of psychological and physical dependence, such as the Severity of Dependence Scale and the Cannabis Use Disorder Identification Test-Revised (CUDIT-R).[108] Use of the CAGE tool for screening for alcohol and substance abuse is also recommended because appropriateness for using cannabis is also dependent on patterns of use relating to other current or past substances of abuse.

Limitations of the Current Research on Cannabinoids

Evidence on indications, benefits, and risks of using cannabinoids continues to evolve. The majority of the clinical studies on phyto- and synthetic cannabinoids had small sample sizes and a relatively short duration of follow-up. A recent systematic review reported that only 21 of the 104 included studies had at least 100 participants per treatment arm, and the median length of these studies was eight weeks.[4,5] There is also a lack of standardization concerning the composition of the cannabinoid administered and the doses used in the studies. Differences in dosing and routes of administration create unique challenges in the interpretation of clinical outcomes. In addition, most studies focus on THC, while CBD and CBN have not been adequately investigated in the clinical context and phytocannabinoid studies in the United States often use dried cannabis supplied by the National Institutes of Health (NIH) with CBD levels of less than 1%.[4] However, there is an increasing interest in CBD and CBN, given their lack of psychoactive properties. Additionally, the variable combinations of THC and CBD from different strains of cannabis and its extracts exert varying physiologic effects. Furthermore, many earlier studies were animal studies, and their results have been extrapolated to humans. This may not be appropriate because there is a significant interspecies variation in the physiologic effects of cannabinoids. As an example, cannabinoids cause tachycardia and postural hypotension in humans but bradycardia in dogs.[109]

Other concerns about the published studies include poor records of the precise dose and duration of cannabinoids consumed by participants. This is an important limitation because participants were often allowed to self-titrate the dose of cannabinoids in these studies. Also, given the high prevalence of polypharmacy in the chronic pain population, the focus for most studies was on the role of cannabinoids as adjuvant analgesics and not as the main analgesic therapy. Finally, there is a paucity of long-term data on the efficacy and safety of cannabinoids for the treatment of chronic pain syndromes.

Legal and Regulatory Considerations

In addition to the evolving science around cannabinoids, legislation and regulatory considerations for the growing, selling, and use of cannabis are also rapidly evolving. At the time of the submission of this chapter, 33 states in the United States, District of Columbia, Guam, Puerto Rico, and United States Virgin Islands have approved comprehensive, publicly available medical marijuana/cannabis programs. Fourteen states allow the limited use of "low-THC/high-CBD" products for medical reasons.[110] Despite the numerous cannabis access state legislations, the U.S. Drug Enforcement Administration (DEA) considers CBD and hemp oils to be a Schedule 1 substance.[111] As per DEA regulations, Schedule 1 drugs have no medical value and a high potential for abuse (e.g. heroin, LSD, ecstasy), and any use outside approved research is considered illegal. The paradox is highlighted by the labeling of cocaine and methamphetamine as Schedule 2 drugs—in other words, these are considered to be less dangerous and to have a greater medical value than cannabinoids. However, in April 2020, the DEA announced that Epidiolex (a cannabinoid used to treat refractory epilepsy) had been descheduled from Schedule V of the Controlled Substances Act.[112] In Canada, Marijuana Medical Access Regulations (MMAR) had provided access to cannabinoids for medical purposes since 2001, and the Cannabis Act legalized the recreational use of marijuana in 2018.[113,114]

Summary of Current Guidelines and Practical Recommendations for the Use of Medical Cannabis

The recommendations around the dosing of cannabis-related products continue to evolve. There is no established dosing schedule for dried cannabis, smoked/vaporized marijuana, and CBD oil. The common guiding principle of titrating cannabinoids is to "start low and go slow," aiming for the maximum potential therapeutic effect while minimizing AE. It is also important to consider regional legislative/regulatory differences in the availability and approval of cannabis-based products and medications.

There are several guidelines and recommendations for the use of cannabinoids for chronic non-cancer pain. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain found weak evidence against cannabinoids for treating neuropathic pain.[115] However, the European Pain Federation (EFIC) and the Canadian Pain Society recommend cannabinoids as third-line agents for the treatment of neuropathic pain based on low level evidence in the literature.[97,116] EFIC recommends the use of nabiximol oromucosal spray for cancer pain as an individual or additive analgesic if opioid or other analgesic agents fail.[97] For chronic non-neuropathic, non-cancer pain, EFIC recommends cannabinoids only in exceptional cases as an individual therapeutic trial. [97] The European Federation of Neurological Societies recommends cannabinoids as third-line therapy in the treatment of central neuropathic pain and spasticity caused by multiple sclerosis (Grade A evidence).[117] The Australian National Drug and Alcohol Council published palliative care guidelines for the use of medical cannabis in 2017.[118] It recommends a trial of 4–12 weeks and subsequent use of medical cannabis if all other standard treatments have failed.[118]

In the recommendations for the use of medical cannabis, the College of Family Physicians of Canada recommends cannabinoids as a third-line agent in the treatment of refractory neuropathic pain and refractory palliative cancer pain based on weak evidence.[119] It strongly recommends against the use of cannabinoids for any other type of pain. It also recommends starting with a prescription medication such as Nabilone or Nabiximols instead of medical marijuana as agents of choice.[119]

Perioperative Use of Cannabis

A recent systematic review and meta-analysis by Abdallah and colleagues studied the analgesic efficacy of cannabinoids on acute pain management postoperatively.[120] The primary outcomes consisted of the cumulative oral morphine equivalent consumption at 24 h and the rest pain scores at 24 h postoperatively. A total of

eight RCTs (924 patients) and four observational studies (4259 patients) were included, offering insufficient data to pool for quantification of differences in cumulative.[120] However, there is evidence of increased pain in patients receiving cannabinoids at 12 h postoperatively and an increased odds of hypotension in the postoperative period.[120]

In a series of discussion articles with contrasting perspectives about the above study, Meeker et al. highlight the lack of evidence for supporting the use of cannabinoids in the acute postoperative pain.[121] It also emphasizes the partially elucidated analgesic mechanism for cannabinoids and its interaction with the endocannabinoid system for acute pain.[121] Clarke et al. argue that Abdallah and colleagues' systematic review and meta-analysis have limited clinical relevance.[122] In fact, some of the drugs and chemical compounds included are not accessible to the public. For details of the limitation of the current literature, please consult *Section 10.Limitations of the Current Research on Cannabinoids.* Clarke et al. suggests for clinicians to consider 1) the potential for cannabis withdrawal; 2) remove the stigma associated with considering all cannabis products as "weed"; 3) education about the eCB system and cannabis products being consumed by patients; 4) consider the potential interactions on anesthetic care associated with the use of plant-based cannabis products.[122]

Conclusions

Cannabinoids have the potential to be a therapeutic option for neuropathic pain and in select and exceptional cases of palliative/oncologic care, but their efficacy has not been established in other chronic pain conditions. Their complex mechanism of action, partially elucidated interactions with the endocannabinoid system, diversified pharmacology, and a choice of multiple routes of administration require ongoing animal and clinical research to allow recommendations to be based on hard data. An understanding of the rapidly evolving science, evidence-based guidelines, and legislations regarding cannabinoids is important for establishing efficacious and safe protocols for their use.

Key Points

- The endocannabinoid system is a complex biologic system composed of endogenous CBR and their respective agonists. It is involved in the regulation of multiple physiologic and cognitive processes in the human body to maintain homeostasis.
- Endocannabinoids are endogenous fatty acid neurotransmitters that are responsible for intercellular signaling. Seven endocannabinoids have been identified to date, but the most studied are AEA and 2-AG.
- CBR are cell membrane GPCR. The most well-known CBR are cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R).
- CBR exist in various locations in the body such as the brain, spinal cord, pituitary gland, thyroid gland, adrenal gland, and digestive system,[13] but their distribution, signaling pathways, and functions are still being elucidated. Please see Table 56.1 for details.
- Phytocannabinoids are natural substances capable of either directly interacting with CBR or sharing chemical similarities with endocannabinoids or both. More than 100 active phytocannabinoids have been identified within the cannabis sativa plant alone.[31]
- Synthetic cannabinoids are chemical molecules that have been designed to possess active pharmacologic properties through activation of CBR. Only two synthetic THC have established clinical applications: nabilone and dronabinol. Nabilone is approved for treating CINV, and dronabinol is indicated for the treatment of AIDS-induced anorexia and CINV.
- Several analgesic mechanisms have been proposed for cannabinoids' analgesic effect on acute, chronic inflammatory, and neuropathic pain. Similar to opioids, cannabinoids act on both the CNS and the PNS. CBR are involved in the transduction, transmission, modulation, and perception of pain in both the ascending and descending nociception pathways.
- A large diversity of cannabis-derived products exist in the market for recreational and medicinal uses. Common ROA include inhalation or smoking via a joint, spliff, pipe, blunt, water-pipe/bong, vaporizing (inhalation), dabbing, e-cigarettes, oral sprays, edibles, drinkables, tinctures (alcohol-based liquid cannabis extracts), other oromucosal/sublingual (e.g. strips and lozenges), transdermal topicals (cannabis-infused lotions, balms, oils), intravenous (syringe), and rectal (suppositories).
- Short-term and long-term use of cannabis may result in significant adverse events affecting the cardiovascular system, the respiratory system, the neurologic system, and the gastroenterology system.
- At the time of the submission of this chapter, 33 states in the United States, District of Columbia, Guam, Puerto Rico, and U.S. Virgin Islands have approved comprehensive, publicly available medical marijuana/cannabis programs.
- The recommendations around the dosing of cannabis-related products continue to evolve. There is no established dosing schedule for dried cannabis, smoked/vaporized marijuana, and CBD oil. The common guiding principle of titrating cannabinoids is to "start low and go slow," aiming for the maximum potential therapeutic effect while minimizing AE.

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57 Topical Analgesics

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In contrast to the use of a systemic analgesic, the use of a topical analgesic may result in pain relief without the requirement for notable systemic absorption.

In certain situations, and with specific agents (i.e. nitroglycerine, fentanyl, clonidine), *transdermal* application results in systemic uptake. In these cases, absorption through the skin while achieving a certain therapeutic blood concentration is responsible for the effects of the drug.

In contrast, a *topical* analgesic requires neither systemic absorption nor a significant systemic concentration to be clinically effective. Its effect occurs when applied locally and directly to the painful areas, with the primary site of action being local to the application site.

Topical analgesics are used for acute pain, as well as for various types of chronic neuropathic and non-neuropathic pain. Different topical analgesics are associated with different mechanisms of action. Using functional neuroimaging, some changes related to topical analgesics can also be seen in the central nervous system (CNS), in addition to effects occurring locally, at the site of application and within the peripheral nervous system (PNS).

Background

A topical analgesic may interrupt specific mechanisms of pain transmission and, by doing so, lead to a reduction in central pain mechanisms and, consequently, perception of pain. As such, skin application of a topical analgesic may reduce activation of the PNS, thus minimizing pain signal transmission and central processing by the CNS. This chapter reviews the use of topical analgesics to treat various painful conditions and provides an update of previously published similar reviews.[1–3]

As topical analgesics are locally applied, without significant systemic absorption, the risk for and severity of significant adverse effects and drug-drug interactions are often less than those for the same analgesic administered systemically.[4] As such, using topical nonsteroidal anti-inflammatory drugs (NSAIDs) versus oral formulations in knee osteoarthritis (OA) may prove effective in limiting the side effects. Rash and unpleasant skin sensations may occur with the use of a topical analgesic, but neither is typically experienced.[5] Among the topical analgesics currently approved by the Food and Drug Administration (FDA) (see Table 57.1) is the 5% lidocaine patch (Lidoderm). Several studies have confirmed the safety and tolerability of topical lidocaine. When using 12 h/day, 5% lidocaine patches demonstrated no significant systemic side effects with plasma lidocaine levels significantly below those known to be associated with cardiac abnormalities.[6] No significant dermal reaction was observed in patients treated long-term with 24 h lidocaine patches.[5–7]

While dermal sensitivity is a potential side effect of all topical analgesics, specific topical analgesics such as capsaicin can be associated with other local adverse effects. After its application, topical capsaicin is commonly associated with severe localized burning. Skin application of capsaicin, at currently available low-dose formulations, does not result in significant systemic accumulation or any life-threatening outcomes; the incidence of burning may decrease with repeated use. However, the occurrence of this side effect may negatively affect treatment adherence and, consequently, the patient's ability to benefit from its use.[8] In contrast to the over-the-counter capsaicin formulations that need to be applied multiple times, the 8% capsaicin patch (Qutenza) can be applied once for 1 h for analgesic effects lasting up to 12 weeks. Qutenza was generally well tolerated in clinical trials even though burning occurred, and the FDA approved it for the treatment of postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy in July 2020.

In patients suffering from chronic pain in addition to other afflictions and comorbid conditions, such as hyperlipidemia, hypertension, coronary artery disease, and diabetes, a trial of topical analgesics may be beneficial in limiting drug-drug interactions, especially if patients have been administered significant amounts of systemic medications for their underlying conditions.[9,10] Since the topical analgesics available typically do not involve dose titration and many systemic agents do, this may provide an additional potential benefit for a patient.

Commercially available FDA approved topical analgesics must have demonstrated to the FDA consistent manufacturing standards and quality control, in contrast to those manufactured and sold by

TABLE 57.1 Food and Drug Administration Approved Topical Medications

Drug	Painful Condition
Lidocaine	Postherpetic neuralgia, intercostal neuralgia, painful diabetic neuropathy
Lidocaine/prilocaine	Postherpetic neuralgia
Diclofenac	Soft tissue injuries, osteoarthritis, musculoskeletal pain
Doxepin	Chemotherapy-induced neuropathy, atopic dermatitis, lichen simplex chronicus
Capsaicin	Painful diabetic neuropathy, human immunodeficiency virus neuropathy, postherpetic neuralgia, postmastectomy pain

a specialized compounding pharmacy. Topical analgesics made by a compounding pharmacy may consist of a combination of substances, such as a local anesthetic, NSAIDs, and anti-depressants combined in a chemical base that is not commercially available and FDA approved topical products. There is no current general requirement for compounding pharmacies to demonstrate manufacturing consistency. However, those compounds are commonly prescribed as almost 1/3 of pain physicians members of the American Society of Regional Anesthesia and Pain Medicine have reported that they prescribe topical analgesics.[11] Topical preparations containing opioids, local anesthetics, anti-depressants, glutamate receptor antagonists, α-adrenergic receptor agonists, adenosine, cannabinoids, cholinergic receptor agonists, gabapentinoids, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor are each at various stages of clinical development.[12]

The mechanism of action of a specific topical analgesic depends on the chemical entity or entities in the specific agent. In the case of the topical agent capsaicin, the mechanism appears to be through agonist activity at the transient receptor potential vanilloid 1 (TRPV1) on Aδ and C-fibers.[13,14] Substance P and calcitonin gene-related peptide are released as a result of this activity. Subsequent depletion of substance P in the C-fibers induces reduced peripheral and central excitability, resulting in less pain through reduced afferent input in response to capsaicin application.[8,13,15] The results of both human nerve biopsy and animal studies demonstrate nerve fiber degeneration in the skin underneath the site of capsaicin application. Such nerve fiber degeneration associated with the application of capsaicin has been suggested to be one of the mechanisms through which its use results in pain relief.[16]

The mechanism of action of a topical NSAID is probably associated with the inhibition of prostaglandin synthesis and the resulting anti-inflammatory effect. However, the extent of the anti-inflammatory effect is not consistently proportional to the pain relief experienced; therefore other mechanisms of action might be considered.[17]

It may be worthwhile to consider the potential benefits of mixed agents with potentially more and synergistic mechanisms of action. For example, the antinociceptive effects of topical morphine may be enhanced by a topical cannabinoid, as demonstrated in studies in rats.[18]

Local anesthetic agents are known to suppress the activity of peripheral sodium channels within sensory afferents and subsequent pain transmission. It has been noted that decreased expression of mRNA for specific sodium channel subtypes may occur following local anesthetic use.[1,5] Several local anesthetic topical analgesics are currently available commercially, including the 5% lidocaine patch, EMLA cream (eutectic mixture of local anesthetics, 2.5% lidocaine/2.5% prilocaine), and the Synera patch (lidocaine, 70 mg/tetracaine, 70 mg). Of these three agents, only the 5% lidocaine patch is associated with an *analgesic* effect without creating *anesthetic* skin, whereas the use of EMLA cream or the FDA approved Synera patch may create both analgesia and anesthesia. This difference among the preparations is useful for application in specific clinical settings, such as venipuncture, lumbar puncture, intramuscular injections, and circumcision, for which creating both anesthesia and analgesia would be helpful.[5]

A novel area of topical analgesic development involves the use of tricyclic anti-depressants as topical analgesics. Certain tricyclic anti-depressants such as amitriptyline and doxepin have been demonstrated to block sodium channels, and the potential clinical benefit of this mechanism when such an agent is topically applied seems to be especially effective in chemotherapy-induced peripheral neuropathy.[19,20] One commercially available topical anti-depressant, doxepin hydrochloride (Zonalon) cream, is currently approved by the FDA for the short-term treatment of adult patients with pruritus associated with atopic dermatitis or lichen simplex chronicus.[21]

Use of Topical Analgesics for Specific Clinical Conditions (see Box 57.1)

Neuropathic Pain

The use of specific topical analgesics for the management of neuropathic pain has been established by several clinical trials that highlight their efficacy.[22–24]

Local Anesthetics

The first medication to receive FDA approval for the treatment of PHN was a 5% lidocaine patch. Initial studies showed that, when compared with patients treated with placebo, patients treated with 5% lidocaine patches experienced statistically significantly more pain reduction in a safe and well tolerated manner.[25,26] Multiple studies have been conducted regarding the clinical efficacy of the 5% lidocaine patch. In an open-label study comparing 5% lidocaine patch with pregabalin (Lyrica) for PHN, the topical local anesthetic was as effective as pregabalin for pain relief in PHN patients. Additionally, the study showed that for patients who did not respond to either the 5% lidocaine patch or pregabalin alone, using these agents in combination resulted in greater benefit and was well tolerated by these patients.[27]

A review that analyzed results from randomized, controlled, and open-labeled studies suggested that the use of 5% lidocaine medicated plaster is effective in the treatment of localized neuropathic pain (LNP), both as part of multimodal analgesic regimen and as a single agent.[28] In a European randomized, double-blinded, placebo-controlled study, 5% lidocaine patch was reported to be effective in mononeuropathies such as intercostal and ilioinguinal neuralgias.[29] The results of this study demonstrated that adding the 5% lidocaine patch to other pharmacotherapeutic regimens could reduce ongoing pain and allodynia within the first 8 h following application over seven days.[29] Use of 5% lidocaine has been included in the international treatment guidelines for treating LNP either as monotherapy or in a multimodal analgesic regimen.[30] Several noncontrolled studies using a 5% lidocaine patch for painful diabetic neuropathy showed pain reduction and good tolerability of this medication.[31–34] Similarly, an open-label study using the 5% lidocaine patch in patients with painful idiopathic sensory polyneuropathy noted significant improvements in both pain and quality-of-life measures.[35]

Topical patches with lidocaine 5% applied to the skin of 150 patients suffering from PHN (up to three patches, 12 h each day) showed reduced pain qualities as described by the neuropathic pain

• Box 57.1 Pain Conditions Treated With Topical Analgesics

Neuropathic pain (various syndromes)
Musculoskeletal pain (acute and chronic)
Soft tissue pain (acute and chronic)
Other pain (dressing changes, cancer treatment related)

scale in a multicenter, randomized, vehicle-controlled study.[36] Of interest was that certain types of neuropathic pain (deep, sharp, and burning) that were reduced had previously been assumed to not be related to PNS but to CNS mechanisms. In the discussion of their results, the authors proposed that given the localized primary PNS mechanism of action of the 5% lidocaine patch, peripheral mechanisms of neuropathic pain might also be important in the development of these neuropathic pain qualities.[36] The results of a functional brain magnetic resonance imaging study of patients with PHN treated with the 5% lidocaine patch for various lengths of time demonstrated that the brain activity occurring with the spontaneous pain of PHN appeared to be modulated in a manner related to the length of application of this medication, thus suggesting again that a peripherally acting agent may have an impact on CNS pain mechanisms.[37]

Another commercially available local anesthetic preparation is the EMLA cream. Its FDA approved indication is for use on normal intact skin for analgesia, but it is not FDA approved for any specific neuropathic pain disorder. Several studies of EMLA cream for the treatment of PHN have reported mixed results. While EMLA cream alone did not show a significant difference in treatment compared to placebo in PHN, it provides excellent analgesia as a pretreatment to 8% capsaicin patch (Qutenza).[38] The results of two uncontrolled studies were more favorable and suggested that the use of EMLA cream could relieve the pain associated with PHN.[39,40]

Capsaicin

Even though there has been interest in using capsaicin for several neuropathic pain disorders such as diabetic neuropathy, painful human immunodeficiency virus (HIV)-related neuropathy, PHN, and postmastectomy pain, many of the older studies had yielded disappointing results, perhaps partly as a result of the weakness of previously available strengths of capsaicin (0.025% and 0.075%), as well as poor tolerance to the treatment and poor treatment adherence, with resulting insufficient pain relief.[41] In contrast, the results of a higher-strength capsaicin preparation demonstrated better analgesia. In one reported study of patients with painful HIV neuropathy treated with 7.5% topical capsaicin cream, the patients experienced notable pain relief but could not tolerate this medication; concurrent treatment with epidural anesthesia was required.[42] High concentration topical capsaicin showed significant relief in patients with HIV-associated distal symmetric polyneuropathy and PHN. The duration of pain relief lasted as long as 48 weeks (PHN), but most commonly 12 weeks.[15,43] A review of the published randomized trials on the use of topical capsaicin for the treatment of either neuropathic or musculoskeletal pain syndromes concluded that it might be useful as an adjunct or sole therapy for a small number of patients who are unresponsive to or intolerant of other treatments.[44] In studies leading to approval by the FDA, the 8% capsaicin patch (Qutenza) was shown to be more effective in reducing pain intensity when compared with an active, lower concentration capsaicin product that served as a placebo. It was also generally well tolerated. In July 2020, the FDA approved the preparation for the treatment of painful diabetic neuropathy. Favorable outcomes have been reported in other neuropathic pain states, such as HIV neuropathy.[45–49]

Other Agents

Topical tricyclic anti-depressants for the treatment of neuropathic pain have emerged as a possible favorable agent. However, evidence has shown mixed results.

A double-blind, randomized, placebo-controlled study involving 92 patients with diabetic neuropathy, PHN, or post-surgical or posttraumatic neuropathic pain, showed no difference in analgesic benefit among any of the four treatment groups (placebo, 2% amitriptyline alone, 1% ketamine alone, or a combination of 2% amitriptyline and 1% ketamine).[50] However, the results of an open-label study completed by the same investigators involving 28 patients with neuropathic pain for six to 12 months treated with the combination topical analgesic 2% amitriptyline and 1% ketamine demonstrated that the average reduction in pain was 34%.[51] In another open-label study using the same type of preparation, the same investigators also demonstrated some encouraging results.[52] More recent evidence established the effectiveness of these preparations for the treatment of PHN.[53]

Noncontrolled trials evaluating the use of topical ketamine in PHN concluded that topical ketamine might be an effective topical analgesic. However, serum ketamine levels were not measured; therefore, it is unclear how "topical" the ketamine preparations were.[54] One report suggested that topical application of geranium oil may provide temporary relief of PHN.[55]

Soft Tissue Injuries and Osteoarthritis

Common musculoskeletal pain conditions include soft tissue injury and osteoarthritis (OA). Since 2007, the FDA has approved three topical NSAIDs for the treatment of these conditions: 1% diclofenac sodium gel (1% Voltaren gel), 1.3% diclofenac epolamine topical patch (Flector patch), and 1.5% diclofenac topical solution (Pennsaid). Each of these FDA approved topical NSAIDs has different indications. Diclofenac sodium 1% gel (1% Voltaren gel) is FDA approved for treating pain associated with OA in joints that can be managed with topical treatment, such as the knees and hands. It has been approved for use as an over-the-counter formulation as of 2020. The diclofenac epolamine topical patch (Flector patch) is FDA approved for the topical treatment of acute pain from minor strains, sprains, and contusions. The diclofenac sodium topical solution (Pennsaid) is FDA approved for the treatment of the signs and symptoms of OA of the knee.[56]

The use of other topical NSAIDs has been studied, most notably outside the United States. A topical ketoprofen patch (100 mg) was found to be superior to a placebo in reducing pain intensity after seven days of treatment in a two-week randomized, placebo-controlled study of 163 patients with pain from an ankle sprain.[57] In a separate study, a comparable topical ketoprofen preparation was evaluated in patients with tendinitis in a randomized, double-blind, placebo-controlled study and found that subjects treated with the active medication fared better than the placebo-treated group with minor skin irritation being only side effect infrequently.[58] Ketoprofen gel has also been shown to be helpful in knee osteoarthritis and was found superior to oral celecoxib.[59] A randomized, open-labeled parallel design trial examined the efficacy of diclofenac patch compared to oral diclofenac for chronic musculoskeletal conditions and found both formulations equally effective.[60] Diclofenac patch has proven efficacious in acute sports injury-related pain in a randomized, double-blind, placebo-controlled study.[61] These results were confirmed in a recent systematic review that included 23 studies and more than 11,000 participants where topical diclofenac proved effective in acute pain such as sprains with minimal side effects.[62] Proved efficacious in many pain conditions, with an excellent safety profile, in April 2020, the FDA approved over-the-counter use of the diclofenac gel to treat acute pain of minor musculoskeletal injuries.

Compared with oral diclofenac, topical flurbiprofen was associated with greater pain reduction and fewer adverse effects in a noncontrolled study of patients described as experiencing "soft tissue pain."[63] Similar findings were reported in a controlled study; the use of topical ibuprofen cream for the management of acute ankle sprains was found to be superior to placebo in reducing pain.[64] In a single-center, randomized, single-blinded, parallel-group study, 5% ibuprofen gel containing 3% levomenthol proved equally effective to 1.16 % diclofenac gel and superior to ibuprofen gel alone for patients acute soft tissue injuries.[65] Placebo and 5% ibuprofen gel administered for a maximum of seven applications showed a significant reduction ($P < 0.001$) in pain intensity plus improvement in physical activities in the study group.[66] Comparing topical with oral NSAIDs, several studies, including a Cochrane database review, showed that topical NSAIDs could provide good levels of pain relief without the systemic adverse effects of oral NSAIDs in the treatment of acute musculoskeletal pain.[67,68]

Topical analgesics proved effective in the treatment of OA.[69–72] A diclofenac patch preparation, studied in a randomized, double-blind, controlled study in patients with chronic pain secondary to knee OA, demonstrated that this patch might be safe and effective for this common condition.[73] A randomized controlled study comparing the use of a topical diclofenac solution and oral diclofenac for the treatment of OA of the knee concluded that use of the topical diclofenac produced relief of symptoms that was equivalent to that of oral diclofenac and resulted in a significantly reduced incidence of diclofenac-related gastrointestinal complaints.[74] A long-term study with the same topical diclofenac solution confirmed its safety during the study period.[75] Individuals with pain in the temporomandibular joint benefit from topical diclofenac solution. The treatment proved effective when applied topically several times daily and was as effective as oral diclofenac. Patients also reported significantly fewer gastrointestinal side effects with the diclofenac topical solution.[76] Placebo-controlled and randomized controlled trials demonstrated the efficacy of 1.16% topical diclofenac gel in patients with painful OA of the knee.[77,78] One meta-analysis examining the use of topical NSAIDs for the treatment of OA found evidence suggesting that topical NSAIDs are more effective than placebo during the initial two weeks of treatment only.[79] The authors concluded that the evidence available indicates that topical NSAIDs are inferior to oral NSAIDs during the first week of treatment.[79] A separate meta-analysis reviewed the evidence for the use of topical NSAIDs for chronic musculoskeletal pain and concluded that topical NSAIDs are effective and safe in treating chronic musculoskeletal conditions for two weeks.[80] Another meta-analysis on the use of topical NSAIDs for OA suggested that of the four studies that compared a topical NSAID with placebo or vehicle in patients with OA of the knee, pain relief did occur for a longer period with the topical NSAID than with placebo but that the results were not uniform for the preparations reviewed.[81]

Patients using over-the-counter preparations often use topical salicylates. Those agents may be associated with significant side effects such as skin irritation. When used excessively, salicylates progress to poisoning that starts with hyperventilation and respiratory alkalosis from direct stimulation of the medulla and progresses to uncoupling of oxidative phosphorylation and resultant lactic acidosis.[82] A randomized controlled study completed in Europe with the topical eltenac examined its effect compared to placebo in 237 patients with knee OA and concluded that the use of topical eltenac for the treatment of OA of the knee is safe and effective.[83] In an additional clinical trial, topical eltenac gel was compared with oral diclofenac and placebo in patients with knee OA. Each active treatment resulted in analgesia superior to that achieved with placebo, and the incidence of gastrointestinal side effects was notably lower in the group treated with topical eltenac gel than in those treated with oral diclofenac.[84] Early discovery studies have demonstrated that topical diclofenac may be effective in reducing the pain associated with various types of degenerative joint disease.[85–87]

Other topical agents have been studied for musculoskeletal pain conditions. However, studies have shown mixed results. In a randomized, double-blind study of 30 patients with temporomandibular joint pain, capsaicin 0.025% cream was determined to be no better than the vehicle (not active) cream.[88] A randomized controlled study of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for OA of the knee showed a significant reduction in pain in the treatment group after eight weeks compared with the placebo group.[89]

Although morphine has been reported as a potential topical analgesic in the management of chronic OA-related pain, the presence of morphine metabolites in urine was identified in treated patients, calling into question how truly "topical" this preparation was, given its systemic effects.[90]

Low Back and Myofascial Pain

Few studies have been published on the use of topical analgesics for low back pain or myofascial pain, two very common conditions. A randomized, double-blind, placebo-controlled study comparing the use of topical capsaicin with placebo in 154 patients with chronic low back pain resulted in 60.8% of capsaicin-treated patients versus 42.1% of placebo patients experiencing 30% pain relief after three weeks of treatment ($P < 0.02$).[91] A multicenter, open-label study involving 120 patients with acute (< six weeks), subacute (< three months), short-term chronic (three to 12 months), or long-term chronic (>12 months) low back pain with four 5% lidocaine patches applied to the most painful areas in the low back region demonstrated that, during the six-week study period, the majority of patients experienced moderate degree of pain relief.[71] A double-blind, placebo-controlled study compared over-the-counter lidocaine 3.6% and Menthol 1.25% patch with 5% lidocaine patch and placebo and showed non-inferiority of the over-the-counter formulation.[91] Additional studies[92] have been published in abstract form, probably because they involve the use of a local anesthetic for conditions not typically thought of as being responsive to this form of treatment.

Other Conditions

Topical analgesics have been used in other painful conditions. However, the number of studies was relatively small. Some topical analgesics, including opiates, may help reduce the pain associated with pressure ulcers or dressing changes.[93–99] Controlled studies have demonstrated the benefit of EMLA cream in reducing the pain associated with circumcision and venipuncture as well as reducing the pain associated with breast cancer surgery.[5,100] At least two studies have suggested that either topical ketamine or topical morphine can be used for mucositis-associated pain following chemotherapy or radiation therapy in patients with head and neck carcinoma.[101,102] Topical opiates have been reported to reduce pain in two children with epidermolysis bullosa.[103] In one report, the observed analgesic effect of menthol, an ingredient common

in many over-the-counter analgesic preparations, is hypothesized to result from activation of κ-opioid receptors.[104] Burn pain has been reported to be treated effectively with a topical loperamide preparation.[105] Two randomized controlled studies showed good efficacy in postoperative pain (diclofenac patch) and wound pain treatment (capsicum plaster topically applied at acupuncture sites).[106,107] Central neuropathic itch was treated successfully with the 5% lidocaine patch in a single case report.[108] The results of an enriched enrollment study in which an open-label initial study led to the randomization of responders in a placebo-controlled study of the use of either 4% amitriptyline/2% ketamine cream, 2% amitriptyline/1% ketamine cream, or placebo in patients with PHN. The study demonstrated that after three weeks of treatment, the average daily pain intensity was lower in patients receiving the higher-concentration combination cream than in those receiving the lower concentration combination or placebo ($P = 0.026$ for the high concentration cream vs. placebo).[109] An open-label study of the use of a 0.25% topical capsaicin agent in a lidocaine-containing vehicle in 25 patients with painful diabetic polyneuropathy and seven patients with PHN demonstrated pain relief in the majority of patients who were studied.[110] In a noncontrolled study of 23 patients with acute migraine headache, 0.1% capsaicin gel applied topically helped reduce mild or moderate pain.[111] In a randomized, double-blind study assessing 154 patients with chronic pain from lateral epicondylitis, topical glyceryl trinitrate (0.72 mg/day) was found to provide statistically significantly greater pain relief after eight weeks compared with placebo.[112] In a study of 52 patients with chronic pain secondary to chronic Achilles tendinopathy, patients who had been treated with topical glyceryl trinitrate for six months were more likely to have less pain and more function than those who had been treated with placebo, three years after treatment ended.[113] Published reports on the use of topical phenytoin for the treatment of pain from superficial burns or chronic leg ulcers are noted as well.[114,115]

Conclusion

Clinicians should consider the use of topical analgesics for a variety of painful conditions. Notably, the number of FDA approved topical agents has increased. Off-label use of the available therapies must include careful consideration of the potential risks and benefits. Repeated observations have shown that topical analgesic use is generally associated with a more desirable side effect profile than oral, transdermal, parenteral, or intrathecally administered analgesics; this factor should be considered when developing a pain management treatment regimen for individual patients, especially when pharmacotherapy is involved. Indeed, additional large, well-designed studies that include comparative trials with non-topical analgesics would be helpful to better understand the role of topical analgesics in the management of acute and chronic pain.

Key Points

- Topical analgesic effects occur when applied locally and directly to the painful areas, with the primary site of action being local to the site of application.
- Topical NSAIDs currently approved by the FDA for soft tissue pain and painful osteoarthritis are 1% diclofenac sodium gel, 1.3% diclofenac epolamine topical patch, and 1.5% diclofenac topical solution.
- Topical lidocaine and capsaicin are FDA approved for neuropathic pain in PHN, with 8% capsaicin approved for painful diabetic neuropathy.
- In contrast to the use of a systemic analgesic, the use of a topical analgesic is less likely to be associated with systemic side effects because the systemic concentration of a topical analgesic is likely to be lower than that with systemic administration.
- Despite the localized, peripheral mechanism of action of a topical analgesic, there may be CNS effects related to topical analgesics.

Suggested Readings

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Psychological Approaches in Pain Management

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Psychological interventions for managing individuals experiencing chronic pain include a wide range of approaches and therapeutic targets. They are based on several theoretical perspectives. This chapter will first provide an overview of the basic principles and backgrounds on which psychological approaches to chronic pain are predicated and then provide reviews of the evidence-based approaches that have demonstrated the greatest empirical support.

From a psychosocial perspective in general, we should differentiate between the concepts of "patient" and "person with chronic pain." "Patient" implies a recipient of treatment in a healthcare setting, whereas a "person with chronic pain" resides beyond the confines of the healthcare system, extending the context into their entire life experience. For the most part, chronic pain is not curable and can persist over extended periods, for years and even decades. Individuals experiencing chronic pain must learn how to adapt and self-manage their lives and any impairments despite the presence of pain.

To illustrate, consider that the primary entry criterion in most clinical trials for pain treatments is moderate pain (usually defined as a pain intensity rating of four or greater on a zero to ten numerical rating scale where zero equal no pain and ten equals the "worst pain possible" or the "worst pain imaginable"). At the termination of these trials, even with "statistically significant" pain reduction by the experimental treatment, the end-point pain intensity is greater than four for most patients. This suggests that people with chronic pain likely continue experiencing at least a moderate level of pain even with helpful treatment. Consequently, it is the individual's intentional efforts that will be required for adaptation and resilience, and those efforts occur largely outside of the purview of health care. For healthcare providers to assist patients in transforming their lifestyle to maximize their ability to manage pain and minimize life disruptions, a good grasp of the chronic pain experience is necessary.

Plight of Individuals With Chronic Pain

People with chronic pain and recurrent, episodic acute pain (e.g. migraine, trigeminal neuralgia) often feel rejected by the very elements of the society that exist to serve them. They typically begin their healthcare journey expecting that there is some physical cause of their pain, that the pathology causing their pain will be identified by a healthcare provider, and that their pain will be eliminated by treatments prescribed by their providers and in a reasonable time interval. In this scenario, the "patient" with chronic pain remains a passive recipient awaiting a "cure" provided by healthcare providers. However, for many of these individuals, the journey becomes an arduous one as they shuttle from one healthcare provider to another, to increasingly invasive laboratory testing, to imaging procedures, to other specialists, and yet more diagnostic tests, all in the quest for an eventual cure. Usual life roles are altered, family and social interactions are impaired, gainful employment may become increasingly difficult, conflicts with third-party payers escalate, and medical expenses for unsuccessful treatments accumulate. They are often informed at various times that no specific pathology can be identified to account for the pain they report and, eventually, that all treatment options are exhausted ("there is nothing else I can do for you"). The perpetual experience of being in the "medical limbo" taxes their patience and perseverance. A frustrated person with chronic pain may lose their faith in health care and feel helpless; psychological distress compounds the difficulty of having to live with chronic pain and disability.

A vicious cycle is initiated when an equally frustrated physician, with no ways to explain the persistence of pain reported and no new treatment options are in sight, may implicitly or explicitly suggest that the pain is caused by "psychological issues." Once optimistic, family members also experience pervasive frustration that adversely affects the family dynamics. Over time, the legitimacy of the pain may be questioned by significant others, employers, and third-party payers, as diagnostic and therapeutic efforts fail despite the sophisticated biomedical technologies. Many individuals with chronic pain feel disbelieved, dismissed, and stigmatized by their situation, which further exacerbates their distress.[1] It is hardly surprising to see the increasing emotional distress that accompanies these people's quest to finding relief.

To place the situation for an individual experiencing chronic pain in context, consider that chronic pain affects over 20% of the adult United States population (50 million), with over 8% reporting high impact chronic pain (limited life or work activities on most days or every day during the past six months).[2] If we extend our view to the impact of chronic pain on families and friends, many more people in our society are affected directly or indirectly by chronic pain. Pain has societal consequences beyond those of the individuals affected. Pain is expensive; health care and indirect costs associated with disability, lost tax revenues, retraining, unemployment or under employment, and legal fees exceed $550 billion annually.[2] These astronomical figures do not incorporate

the incalculable human suffering attended to chronic pain. To put it bluntly, pain hurts the individual with the symptoms, people around the person, and society as a whole. The Institute of Medicine aptly labeled the current situation of chronic pain as a "crisis."[2]

Despite an increased understanding of the pathophysiology of pain, technologic advancements, and pharmacotherapeutic innovations, a *cure* for chronic pain has eluded the best efforts and intentions of researchers and healthcare providers. Regardless of the treatment modality, the pain reduction averages only about 35%, and fewer than half of persons treated obtain this outcome. The extent of improvement in emotional, physical, and social functioning is often below this level.[3]

People with chronic pain continually confront noxious symptoms and experiences that affect every aspect of their lives. Thus those with chronic pain face a dire need to manage their symptoms. Recall Bonica's comment in the preface of the first edition of his seminal work The Management of Pain over 60 years ago:[4]

> *"The crucial role of psychological and environmental factors in causing pain in a significant number of patients only recently received attention. As a consequence, there has emerged a sketch plan of pain apparatus with its receptors, conducting fibers, and its standard function, which is to be applicable to all circumstances. But . . . in so doing, medicine has overlooked the fact that the activity of this apparatus is subject to a constantly changing influence of the mind." (p. 11)*

It should be evident that psychological, social, and contextual factors play significant and contributory roles in the experience, maintenance, and exacerbation of pain. The neurophysiology does not exist apart from psychology and the context in which pain occurs. Instead, what we do, how we think, and how we feel constantly send feedback to the brain to modulate the neurophysiologic system. Psychological processes such as emotional states, thoughts about pain, and attitudes in response to pain may impact on, and be affected by, how an individual interprets, perceives, and manages his or her pain.[5]

With the advent of innovative research, we have become aware that psychological factors are interconnected with brain regions implicated in the perception, attention, and modulation of pain.[6,7] In this sense, research has shown that it is not the pain itself but rather the interpretation of the pain that predicts how an individual behaves in response to it. How others respond to people with pain can affect the experience of pain, adaptation, and disability. These observations are the basis for the emergence of interest in using psychological approaches to assist individuals in managing their pain and lives despite pain.

Psychological Formations of Chronic Pain

To many healthcare providers, "psychological treatment" is a generic term. However, various psychological interventions form the basis for a diversity of psychological treatments based on their tenets. Although all psychological treatments have a fundamental commonality, emphasizing the whole person affected and self-management rather than cure, they do have essential differences. A brief review of the history of the area is warranted to provide a better understanding of the current practices of psychological interventions with individuals experiencing chronic pain. This is important for non-mental health professionals for their treatment planning and making referral requests about which psychological treatment to select from among those available. Since there are different emphases among the various treatments, providers need to identify and select a treatment approach that best fits each of their specific patient's current state, most pressing problems, and personal characteristics. However, depending on resources, there may be limitations and constraints on the options available.

Psychogenic View

As is often the case in medicine, when physical explanations seem inadequate and no treatments seem to provide consistent outcomes, individuals' reports of pain are often attributed to a psychological origin (i.e. psychogenic). This unfortunate trend in medicine has a long history but was first systematically articulated in the 1960s when people with persistent pain were viewed as having compulsive and masochistic traits, inhibited aggressive needs, and feelings of unresolved guilt—"pain-prone personalities."[8] It was commonly believed that people reporting persistent pain had histories of troubled childhoods, including emotional abuse, family dysfunction, loss of parents, and pressure to attain unreasonably high goals for themselves.[9] Some have insinuated the psychogenesis of pain from the psychological "wounds" by linking childhood trauma to adulthood chronic pain, although the findings to support this contention are not consistent and remain controversial.[10,11]

The psychogenic model has focused clinicians' efforts toward identifying the etiologic and historical psychopathologic processes involved. Addressing the maladaptive psychological needs that allegedly caused pain was common in the early days of pain medicine.[12,13]

Although the incidence of depression and anxiety are common in people with chronic pain, and how could they not be given the description of the plight of the person with chronic pain outlined, attempts to establish the causal link have been inconsistent.[14] To address the gap, the American Psychiatric Association formulated a psychiatric diagnosis, "Somatoform Pain Disorder," in their 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[15] The diagnosis of Somatoform Pain Disorder was made by default when persistent pain could not be explained biomedically, and the pain was associated with excessive thoughts, feelings, or behaviors about the symptoms. This diagnostic category was highly criticized for the questionable meaning of "medically unexplained" pain and appropriateness of the assumption that poorly defined "excessive distress" has an etiologic role in pain.[16] The classification was deleted from the latest version of the diagnostic manual and replaced by a new designation, Somatic Symptom Disorder. Notably, in this new iteration, pain is no longer required to be "medically unexplained."[17] Nevertheless, it remains unclear how the diagnosis leads to appropriate treatment plans, and it continues to risk misdiagnosing a medical condition as a psychiatric illness.[16] For the most part, the psychogenic model has thus come under appropriate scrutiny and has fallen out of favor.

Behavioral Formulations

Learning principles play an important role in dysfunctions associated with chronic pain. Three behavioral principles can influence people with chronic pain individually and interactively. Through experiential learning based upon the classical (Pavlovian) conditioning model, a painful experience can lead to an emotional association between contextual factors and activity with fear of pain. For example, for a person who tries to vacuum rugs and then experiences a pain flare, the co-occurrence of vacuuming the floor and the resulting pain becomes conditioned to pain-related

fear. Avoidance is a natural response to feared activity. Pain-related fear-based conditioning is ubiquitous in chronic pain, leading to further deconditioning and loss of function. The Fear-Avoidance Model has incorporated the conditioned fear and avoidance into a vicious circle of pain, avoidance of activity, and subsequent deconditioning and the resulting disability.[18] Several studies have shown the significant association between pain-related fear-avoidance and disability.[19–21]

Another contribution of the learning principles to pain comes from the operant conditioning model, pioneered by Fordyce at the University of Washington in the 1970s.[22] The operant conditioning model posits that the likelihood of particular behavior recurring depends upon the immediate consequence of the behavior. For example, imagine that a man grimaces and complains of his back pain while arguing with his wife. The wife immediately stops arguing, brings him a cold beer, tells him to take it easy, and rubs his back. Here, the likelihood of grimacing and complaining reoccurring will increase because of immediate consequences of (1) negative reinforcement (removal of the aversive situation) and (2) positive reinforcement (attaining something positive: beer, sympathy), and a back rub. Fordyce posited that over time, various pain-related behaviors (e.g. sighing, moaning, bracing, limping, guarding, medication taking) could be reinforced through operant conditioning and, consequently, shaping and maintaining the person's chronic pain experience.

From the operant perspective, the central features of pain behaviors are that behavior is (1) a source of communication and (2) observable. People express their pain in different ways. Their significant others respond to those expressive behaviors in different ways. However, the principles of operant conditioning apply to all behavioral communications. Maladaptive behavioral patterns that are reinforced could lead to significant disability and increased healthcare utilization.[23] Consequently, identifying maladaptive patterns of reinforcement and replacing them with adaptive patterns to reinforce "well behaviors" (e.g. activity, reduced time reclining) is a critical focal point of behavioral treatment of individuals with chronic pain.

Fordyce's operant conditioning model does not concern itself with the initial cause of pain. It also does not directly address pain per se, which is a subjective and perceptive experience. Instead, it focuses on observable behaviors presumably related to the communication of pain and subsequent reinforcement. Observable behaviors help people with chronic pain communicate with the world around them, but they can lead to greater dysfunctionality if maladaptive behaviors are continually reinforced and maintained.

However, it is important not to mistakenly view pain behavior as synonymous with "malingering." Malingering is a psychiatric and legal construct that involves consciously and purposefully faking symptoms for personal gain. Operantly conditioned behaviors are neither intentional nor faked, and people do not explicitly use operantly conditioned behaviors—pain behaviors—to obtain something they value and desire.

The third learning principle is encapsulated in the social learning model. The principle of social learning emphasizes that behaviors can be learned not only by actual experiential conditioning but also by observation of what others do, how they are responded to, and how they respond themselves. For example, a middle-aged man might learn how to act when a pain flare occurs by observing how other middle-aged men in similar circumstances act. This type of learning is ubiquitous in our lives, from a baby learning how to react to stress by observing her parents to popular figures and social media shaping cultural norms. Consider the case of the television series, "House." The central figure, Dr. Gregory House, demonstrates how he responds to his chronic pain—he exclusively and excessively takes analgesic drugs. Thus we can acquire responses that were not previously in our behavioral repertories by observing others. We learn not only observable behaviors but also briefs and attitudes from others. Our response to pain is no exception. Expectations and behavioral responses to nociceptive stimulation are based, at least partially, on one's social learning history,[24] and expectations play an important role in shaping the pain experience.[25]

Understanding social learning history is clinically important in pain medicine. Children develop attitudes and expectations about health and health care from their parents and other close adults. This lets them learn how to appraise somatic signals and respond to pain. Research has shown that children of parents with chronic pain show greater pain-related behaviors during stressful times than children of healthy parents.[26,27] It has also been demonstrated that people can acquire physiologic responses to pain by observation.[28]

Gate Control Theory

Though not a psychological formulation itself, the Gate Control Theory (GCT)[29] popularized the importance of central psychological factors in pain perception. The GCT has revolutionized thinking about nociceptive processes and the perception of pain. Melzack and Casey differentiated three systems related to nociceptive processing: sensory-discriminative, motivational-affective, and cognitive-evaluative—all contributing to the eventual experience of pain perception.[30] The GCT contradicts the dualistic notion that pain is either somatic or psychogenic. Instead, it postulates the physiologic basis of the psychological factors modulating the pain experience.

The GCT was the first integrated model of pain. Before this, psychological processes were largely dismissed as a reaction to pain. The GCT specifically points to the psychological factors as significant moderators of pain. Although the physiologic details of the GCT have been challenged,[31] its impact on pain research has been substantial. It also became a source of inspiration for technologic and clinical applications, such as neuromodulation, pharmacotherapy, and multimodal approaches to treating pain.

Cognitive-Behavioral Perspectives

The cognitive-behavioral (CB) perspective is a broad psychological model integrating many of the aforementioned behavioral, emotional, social, and cognitive factors.[32–34] The model focuses on the cognitive factors as a driver of one's emotional, context, and behavioral experience, forming a dynamic personal psychosocial environment that interacts with chronic pain experience.[35] It suggests that negative cognitive constructs such as fear appraisals, catastrophizing, beliefs about helplessness, and protective factors such as resilience and self-efficacy can affect the experience of pain. The model posits that cognitive processing is more influential than sensory activity in how individuals perceive, interpret, and manage their pain.[35,36] Treatments based on the CB perspective are directed not toward a cure but rather toward addressing the negative appraisals and interpretations, encouraging positive beliefs about self-efficacy, fostering resilience, and encouraging adaptive behaviors despite the persistence of pain. A set of techniques, described below, are used to achieve these ends.

To illustrate the potential of cognitive factors, consider the case of a person waking up with abdominal pain. She would make use of her prior experiences and cognitive ability to try making sense of this new sensory experience. If she attributes the pain to her rigorous work out at the gym yesterday versus if she thinks of a family history of colon cancer, her emotional response and the actions she takes would be very different. The thought process often serves as filters that determine the meaning of the experience and the appropriate responses. Thus threatening thought processes will likely lead to negative emotions, a sense of being overwhelmed and distressed, whereas a more benign interpretation might have relatively little impact.

Biopsychosocial Model

The biopsychosocial model integrates and expands both the GCT and CB perspectives of pain, viewing chronic pain as an outcome of dynamic interactions among and within the biologic, psychological, and sociocultural variables.[37,38] It accepts the idiosyncratic nature of such dynamicity yet provides a conceptual framework to work with a range of people with chronic pain. Initial pain onset may have driven all the systems at first, but then, each system influences other systems reciprocally—maladaptive momentums of how the dynamic interaction lead to further disability and distress. From the biopsychosocial perspective, physiologic, psychological, and social factors each make important contributions throughout the trajectory of pain. However, the relative contributions of each may vary over time, with biologic factors making a larger contribution during the acute phase, the roles of psychological and social factors increase as the presence of pain persists. The biopsychosocial model has become a basis of multimodal approaches in pain medicine, as the model indicates that pain is a multifactorial phenomenon and addressing just one area will likely yield unsatisfactory outcomes.

Referral for Psychological Intervention

Ideally, attention to psychosocial factors is considered for all patients with persistent pain. A comprehensive psychosocial assessment may be beyond the purview of primary care providers, even when they acknowledge the importance of psychological and social contributors. Thus the healthcare provider should sometimes consider a referral of psychological assessment and treatments as part of a comprehensive treatment plan. The healthcare provider should be alert for red flags that may serve as an impetus for referral for a more thorough evaluation by a mental health professional who specializes in the treatment of pain.

Box 58.1 lists a general set of questions worth considering by primary care providers for patients who report persistent or recurring pain that may help guide decisions regarding more comprehensive psychosocial evaluation. Positive responses to these questions should not be considered sufficient to make a referral for more extensive evaluation, but when more than six or seven are positive, referral should be considered. These questions should not be viewed as a replacement for a more comprehensive psychosocial evaluation but rather as screening questions that should be routinely included when interacting with chronic pain patients during a discussion of their history. They may help identify those patients who might be considered candidates for referral for a psychosocial evaluation. Chapter 15 provides a discussion of what is typically included in a comprehensive psychosocial evaluation when it is determined that such an evaluation is warranted.

• BOX 58.1 Screening Questions[a]

Has the patient's pain persisted for three months or longer despite appropriate interventions and in the absence of progressive disease? [Yes]

Does the patient repeatedly and excessively use the healthcare system, persist in seeking invasive investigations or treatments after being informed that these are inappropriate, or use opioid or sedative-hypnotic medications or alcohol in a pattern of concern to the patient's physician (e.g. escalating use)? [Yes]

Does the patient come in requesting specific opioid medication (e.g. hydromorphone [Dilaudid], oxycodone [OxyContin])? [Yes]

Does the patient have unrealistic expectations of the healthcare provider or the treatment offered ("total elimination of pain and related symptoms")? [Yes]

Does the patient have a history of substance abuse, or is he or she currently abusing mind-altering substances? [Yes]

Patients can be asked, "Have you ever found yourself taking more medication than was prescribed, or have you used alcohol because your pain was so bad?" or "Is anyone in your family concerned about the amount of medication you take?" [Yes]

Does the patient display a large number of types of pain behavior that appear to be exaggerated (e.g. grimacing, rigid or guarded posture)? [Yes]

Does the patient have litigation pending? [Yes]

Is the patient seeking or receiving disability compensation? [Yes]

Does the patient have any other family members who have had or suffer from chronic pain conditions? [Yes]

Does the patient demonstrate excessive depression or anxiety? [Yes]
Straightforward questions such as "Have you been feeling down?" or "What effect does your pain have on your mood?" can clarify whether this area needs more detailed evaluation.

Can the patient identify one significant or several stressful life events before symptom onset or exacerbation? [Yes]

If married or living with a partner, does the patient indicate a high degree of interpersonal conflict? [Yes]

Has the patient given up many activities (e.g. recreational, social, familial, in addition to occupational and work activities) because of pain? [Yes]

Does the patient have any plans for renewed or increased activities if the pain is reduced? [No]

Was the patient employed before the onset of pain? [No] If yes, does he or she wish to return to that job or any job? [No]

Does the patient believe that he or she can ever resume normal life and normal functioning? [No]

[a]If there is a combination of more than six "yes" answers to questions one to 13 and "no" answers to questions 14 to 16 or if there are general concerns in any one area, consider referral for psychological assessment.

Psychological Interventions

As we noted, psychological treatment is a generic phrase that encompasses a range of interventions based on conceptual models that are not identical and with different emphases. The approach taken by any mental health professional will be based on his or her adherence to the specific theoretical model described above.

Insight-Oriented Therapies

Insight-oriented therapies rely on psychogenic and psychodynamic concepts of human development and focus on the early relationship experiences of the individual. Within the context of the therapeutic relationship, maladaptive experiences are reconstructed with an intent to help patients to redo the experiences in a "correct" way.[9] Patients attain insight into their own emotional needs and motivation through interpreting their therapeutic relationship. It is unclear as to how common this approach is used for chronic pain.

Empirical evidence supporting the psychogenic view is lacking. This is not to say that insight-oriented therapies have no role in treating people with chronic pain, and there may be some who might benefit.[12] However, insight-oriented psychotherapy has not been shown to be particularly effective in reducing symptoms in most patients with chronic pain. Furthermore, studies have suggested that the emotional distress observed in people with chronic pain typically occurs in response to pain[39,40] and may resolve once the pain is treated adequately. Furthermore, prior maladaptive experiences may not play a significant role in the maintenance of chronic pain.[41]

Behavioral Approaches

Extinction/Exposure Intervention (EI)

Based on the conditioning model described, EI is predicated on a paradigm designed to disconnect the association between pain and fear and the subsequent avoidance of functional activities. Treatment begins with a thorough identification of avoided behaviors that are associated with subjective emotional distress. Clinician and patient work together to develop a hierarchical list of avoided activities based upon the level of emotional distress associated with each activity. Clinicians provide education on the behavioral principle of conditioning and how EI will lead to better physical and emotional functioning. Exposure to feared activities will then follow, in a graded fashion, from the bottom of the list of avoided behaviors (those causing the least degree of emotional distress) and workup toward the tasks with greater emotional distress. As the patient moves up the list of feared activities, he or she will be encouraged to relax to reduce the accompanying emotional arousal and reducing the fear associated with the specific activity that has been avoided. The key to the EI is direct experience and repetition. A person will engage in avoided behavior until the emotional distress that was initially attached to the task diminish in a clinical setting at first, but it may be extended to the individual's natural environment through home practice.

EI is experiential by nature, and it leads to behavioral modification by providing a powerful disconfirmation of assumed risks associated with the avoided tasks. An important behavioral concept is a generalization where responses to an initial stimulus, such as a specific activity, will be extended to stimuli (e.g. activity) that are perceived as similar. So, in the case of avoidance of a specific activity may be extended to related activities and thereby lead to increased functional limitations and physical deconditioning, further escalating functional disability.

Although EI is considered a "behavioral" approach, its effects extend to cognitive and emotional domains. A recent randomized control trial for people with back pain with a session by session analysis has revealed that EI and CBT, described below, share the same psychological processes.[42]

Studies evaluating the EI have shown a significant decrease in pain and functional limitation in a range of pain conditions in adults, including back pain,[42–44] complex regional pain syndrome (CRPS),[45] posttraumatic neck pain,[46] and upper-extremity pain.[47]

However, as with all psychological interventions, EI is not for everyone. The contraindications include the use of benzodiazepine. The successful extinction of the pain-fear-avoidance link depends upon the full experience of conditioned fear, which can be attenuated by medication, leading to incomplete extinction trials. Some people may feel comfortable working through fear in this way. Some thoughts should be given to careful patient selection.

Operant Approach

The aims of the operant approach are two-fold: to diminish the positive consequence for pain behaviors and reinforce "well behaviors" (e.g. physical activity, positive social interactions, open communication). The operant approach does not address pain intensity directly; instead, it focuses on guiding people away from maladaptive pain behaviors and moves them toward behavioral patterns of wellness. A careful behavioral analysis to delineate how people communicate their pain and how such communications are responded to (i.e. reinforced) sets up a treatment target.

For example, consider a case where every time a woman complains of pain, her children tell her to go rest, and they take over specific household chores. The behavioral analysis reveals that the verbal complaint of pain is rewarded by her children, giving her attention and encouraging her to rest (positive reinforcement) and by her avoiding responsibility for household chores (negative reinforcement). A clinician could work with the patient and her children to help them understand this contingency and modify the women's response. The children do not have to be unsympathetic, but they no longer should encourage her to rest and take over her chores. The clinician and the family can work to come up with responses acceptable for both. Another example is the use of medication on an as-needed basis (as illustrated by the television character referenced above, Dr. House). To reduce the pharmacologically mediated reinforcement (e.g. reduced distress and pain), time-contingent use of medication (i.e. scheduled regardless of current pain intensity) is encouraged in the operant-based program. Similarly, the operant program discourages pain-contingent activities (e.g. ceasing activity because of increased fatigue rather than planned rest intervals). The pain levels typically fluctuate, but the operant approach discourages changing the activity level based solely on pain. Instead, the program sets specific goals in a graded fashion for people to increase their physical function, regardless of pain levels.

It is helpful to remind patients treated with operant conditioning that changing the reinforcement contingency can temporarily increase the maladaptive behaviors they are trying to eliminate. It is called behavioral "potentiation," a phenomenon of increased target behaviors when reinforcement is withdrawn. Many people become discouraged by the escalated behaviors they are trying to work on. It is important to help them understand that this is expected and will dissipate as long as they adhere to the operant regimen and their physical conditioning improves.

The efficacy of operant treatment has been demonstrated in several studies for persons with low back pain[48] and fibromyalgia.[49] Behavioral principles are often incorporated as a part of multimodal approaches (e.g. physical therapy, interdisciplinary rehabilitation programs). However, as noted with ET, not all patients respond well to operant treatment, and research is needed to identify the characteristics of those who are likely to derive the greatest benefit.[50]

Cognitive-Behavioral Therapy (CBT)

CBT is the most accepted, mainstream psychological intervention for people with chronic pain. However, it is extremely important that CBT not be confused with a specific set of cognitive and behavioral *techniques*. The CB perspective focuses on the objectives of self-management and resilience. A variety of cognitive and behavioral techniques are often used to accomplish the objectives.

One of the primary assumptions of the CBT is that pain-related functional disability in chronic pain is linked to those

• BOX 58.2 Assumptions of the Cognitive-Behavior Perspective

- People are active processors of information and not passive reactors.
- Thoughts (e.g. appraisals, expectations, beliefs) can elicit and influence mood, affect physiologic processes, have social consequences, and serve as an impetus for behavior; conversely, mood, physiology, environmental factors, and behavior can influence the nature and content of thought processes.
- Behavior is reciprocally determined by individual *and* environmental factors.
- People can learn more adaptive ways of thinking, feeling, and behaving.
- People should be active collaborative agents in changing their thoughts, feelings, behavior, and physiology.

experiencing chronic pain's sense of helplessness in managing their pain. Thus treatment goals focus on helping these individuals realize that they can acquire adaptive coping skills and apply them to manage pain and enhance resilience despite physical symptoms and impairments. Although there is no specific CBT protocol that all therapists follow, all CBT approaches share the goal of increasing a sense of self-efficacy for actively managing their pain. Typically, CBT includes modifying the maladaptive cognitive process, acquiring behavioral skills, and incorporating a CBT lifestyle. The assumptions underlying CBT are listed in Box 58.2.

Cognition is a powerful mediator of our behaviors and emotions. Therapists can use simple examples to demonstrate the mediating effect by using a contrasting example. Consider the two types of thoughts following a pain flare: what would be the consequence of (1) if a woman believes this means she will never, ever, get better versus (2) if a woman thinks that although this is a challenge, she can still do many things today and see that with effort she may be able to do more desired activities if she tries to self-manage her pain, its impact, and her life. During CBT, a fair amount of time is spent helping patients understand the effects of maladaptive, negative, and often extreme thought processes, such as catastrophizing and dichotomous (black/white) thinking. Patients will then be directed to note how they respond to stress and pain to identify their own maladaptive thoughts. They are then taught to challenge the thoughts ("Am I sure I know that my pain is never going away? On what am I basing that assumption"?) and to come up with alternative thoughts ("what I am sure is, although I am uncomfortable now, I just do not know if the pain will continue forever. Maybe I can practice some stretching and see if this helps").

People with persistent pain often have low expectations about their own ability to manage pain and see themselves as helpless. Such negative appraisals lead to demoralization, inactivity, procrastination, and over-reaction to pain and stressors. Challenging such negativity and finding alternative appraisals can empower patients to transfer from a passive recipient of care to an active participant in pain management.

Along with the modification, the acquisition of behavioral skills is critical in helping patients cope better with pain and stress. There are several skills-training protocols for communication skills, coping skills, problem solving, autonomic skills (relaxation), behavioral rehearsal, time management, pacing, distraction, imagery, and meditation. Note that with CBT, as operant and EI interventions, the goal is not to eliminate stress and pain. Be realistic and help patients become self-efficient in re-regulating their physiologic and emotional responses through cognitive and behavioral skills. Individuals vary greatly in their aptitude and preference for various skills. There is no one skill training that works for everyone. Clinicians may need to try out a few options and ultimately customize the skill training for the specific needs of individuals to optimize the therapeutic benefit.

CBT will not be beneficial if it does not become a part of individuals' lifestyles. The integration of skills in life is critical for the successful implementation of CBT. Thus a key element of CBT is home practice. Intensive monitoring of symptoms, thoughts, behaviors, and emotions at home is needed at the beginning to delineate the areas of therapeutic targets. As patients advance through the therapy, they are expected to apply the skills to daily life situations. Subsequent treatment sessions (in-person, technologically delivered, individual or group) gradually become the time to review, troubleshoot, and refine the skills. This process of generalizing the skills outside of the clinic becomes the vehicle of sustainable, long-term benefit.

We have described CBT in some detail as it is perhaps the most frequently evaluated psychological approach in pain medicine with a great deal of replicated support demonstrating the efficacy for treating various chronic pain conditions in adults and children.[51–53] Imaging studies have shown that CBT significantly alters cortical density/volume in people with various pain conditions.[54,55] The effects of CBT are more pronounced when CBT is tested against treatment as usual or wait-control than when compared to active control (e.g. psychoeducation). However, the interpretation of these reviews is somewhat confusing as they include the trials with CBT alone and CBT and other modalities.[56] Generally, when CBT is provided alone without other daily, effect sizes on maladaptive thoughts and emotional distress are low to moderate, but effects are limited for pain reduction.[57] Most often, CBT is integrated within more comprehensive rehabilitation programs. CB principles have been adapted and used by nurses and physical therapists as well as being directly provided by mental health professionals.[58]

CBT and Interdisciplinary Rehabilitation

Studies evaluating interdisciplinary pain care programs typically include medication management, physical therapy, and CBT. Interventional procedures may be included. The fundamental premise of this integrated multimodal approach is of the biopsychosocial, CB perspective in which clinicians try to assist patients to become proficient in managing their pain via improving physical functioning and coping skills. Comprehensive and concurrent treatment plans may include drug tapering or adjusting, exercise and other physical therapy modalities, and behavioral medicine components to improve cognitive and behavioral skills.

The interdisciplinary pain treatment is the most evidence-based approach in pain medicine. A large volume of empirical outcomes exist that support the effectiveness of the interdisciplinary approach to pain for improving pain, physical functioning, mood, work functioning, and healthcare utilization[59–62] with evidence for long term sustainability of the benefit.[63,64] [For a more extended discussion of rehabilitation see Chapter 60.]

Acceptance and Commitment Therapy (ACT)

ACT is a variation of CBT that integrates mindfulness (described below), diffusion of inflexible cognition, acceptance of pain, and value-based behavioral activation.[65] A central premise of ACT is not to focus on controlling pain. ACT involves acceptance of pain through mindfulness training and identification of life activities

important to them. ACT education attempts to help people experiencing pain to understand experiential avoidance: a tendency to avoid a certain activity because it brings aversive feelings (e.g. anxiety, fear) even though the activity can lead the person to achieve the goal they would like in life. For example, a child who avoids going to school because she does not know how to deal with peers and worries about what others think of her, even though going back to school is a critical activity to achieve her goal of going to college. Experiential avoidance is common in chronic pain. It is often misunderstood as a lack of motivation or being lazy on patients' part when the lack of progress toward a goal is encountered in treatment. It is helpful for clinicians to evaluate the possibility of experiential avoidance; ACT is one treatment modality that directly addresses it.

Chronic pain experience often limits both the physical and social domains of a person's life. Rehabilitation and recovery do not necessarily mean they return back to life as it was prior to the pain onset. Establishing a "new normal" requires a readjustment of expectations from self and others and navigating through how patients portray themselves to the world. ACT therapists work on the psychological process called "psychological flexibility,"[66] defined as the ability to adapt to situational demands by modifying behavioral or psychological repertories to achieve a goal that the person values. ACT addresses maladaptive cognition to aid this process, as in CBT; however, whereas CBT disputes negative cognitions, ACT accepts it and attempts to "defuses" them.

ACT has been shown to outperform the United States Food and drug administration—approved pharmacotherapy in treating fibromyalgia.[67] As in the case with CBT, ACT seems to achieve clinically meaningful benefit in multiple outcome domains when integrated as a part of a multimodal, interdisciplinary treatment program.[68–70] A recent systematic review has demonstrated that interdisciplinary programs with ACT would yield a significantly greater effect size for physical functioning, psychosocial impact, and mood than ACT alone.[71]

Despite some reported positive results, meta-analytic research has concluded that ACT and mindfulness-based approaches do not show clear superiority to more traditional CBT across studies but remain viable and comparably effective interventions for chronic pain.[72,73] The relative lack of distinction between the benefits of ACT and other approaches may also be because of non-specific therapeutic factors resulting in a blurring of these treatment mechanisms; a recent study reported significant increases in pain acceptance after completion of a predominantly CBT-focused multi-disciplinary care program.[74]

Mindfulness-Based Stress Reduction (MBSR)

MBSR is a collection of meditative techniques designed to minimize stress response through mindfulness exercises often used within ACT. As a part of the training, people are taught to accept bodily experiences, regardless of averseness, as naturally occurring experiences. When applied to chronic pain, this approach emphasizes the importance of accepting pain as something natural. It aims to reduce the threat value of pain and thereby modifies the emotional reaction to pain.

The central objective of mindfulness meditation is to enhance one's awareness of the entire perceptual field. It incorporates focused attention and whole-filed awareness in the present moment. Individuals are encouraged to experience pain by simply observing it without judgment, thoughts, and emotions, as it comes moment by moment.[75] The belief is that physical pain will be transformed from something feared into an object to be investigated, experienced, and explored through mindfulness meditation.[76] There is no universally accepted definition of mindfulness and the underlying factors that constitute this concept. Thus comparisons between different studies exploring mindfulness may be inappropriate because of mindfulness being measured, taught, and practiced in different ways across these studies.[77]

Thus the evaluation of MBSR outcomes is difficult because there are so many variations of approaches and techniques. Another problem is the general weakness in the methodologic rigor in research evaluating MBSR. Several systematic reviews concluded that the effectiveness of MBSR could not be conclusively stated because of the poor quality of the studies.[73,78–81]

Not all outcomes are discouraging. A recent parallel randomized trial showed MBSR to CBT to have a comparable benefit that was superior to outcomes of the treatment as usual group.[82] It will take some more accumulations of evidence from rigorous studies, however, before we can confidently evaluate the effectiveness of MBSR for treating chronic pain.

Other Psychological Techniques

Several psychological techniques and skill training procedures can be used to treat people with chronic pain. These tools are often included as a part of a comprehensive CBT or ACT approach described. Here, we briefly describe some of the commonly used techniques.

Controlled Breathing and Relaxation

Inability to properly regulate stress response and is common in chronic pain patients.[83] It is frequently observed that people with chronic pain complain that "I can never relax." There are many types of relaxation exercises, and no evidence to substantiate any of them is more effective than any other. Relaxation training helps people to achieve a psychophysiologic state of relaxation and manage hyperarousal. Relaxation training has an entirely different connotation from the general term "relax." Many people equate relaxation to doing nothing. Relaxation training, however, is an active practice where people learn to pay attention to their bodily state to modify tension levels actively. Breathing techniques, particularly diaphragmatic breathing, stimulate the parasympathetic nervous system via activation of the vagus nerve.[84] There are several relaxation and breathing techniques. For those who are interested in the technical aspects of those training, see these handbooks.[85,86]

The relative rarity of using relaxation skill training as a sole treatment modality to treat chronic pain makes it difficult to gauge its clinical benefit as a unimodal approach because they are often included within interdisciplinary treatment programs and are incorporated in the ET and CBT. Generally, the outcomes for relaxation are positive, albeit modest.[87,88] However, the effect seems to be time-limited.[89] Furthermore, there are several methodologic challenges in designing rigorous trials to test breathing, making it challenging to establish conclusive benefit.[90]

Biofeedback

Developed in the 1960s, biofeedback is a self-regulation technique that has been used to successfully treat several chronic pain states, such as headache, back pain, chronic myofascial pain, and irritable bowel syndrome.[91,92] The objective of biofeedback is to teach people to exert control over their physiologic processes, which are

believed to be involved in symptoms such as headaches, back pain, and pain associated with temporomandibular disorders.

Biofeedback uses electrical sensors on the skin over muscles to detect this rising tension. The electrical sensors are linked to the biofeedback machine, which provides audible or visual signals to the patient. These signals enable people to understand their physiologic activities and control them consciously and, over time, more automatically. With experience, people can determine what mental or physical adjustments produce the greatest reduction in tension. They may then use these exercises with no biofeedback machine.

As noted, during biofeedback, the patient is connected by electrodes to equipment linked to a computer that records physiologic responses. These processes may include skin conductance, respiration, heart rate, heart rate variability, skin temperature, brain wave activity, and muscle tension. The recording equipment amplifies and converts the readings into visual or auditory signals on a monitor that the patient can observe. In this way, the information recorded is "fed back" to the person, which potentially helps the individual learn to change physiologic responses by manipulating the auditory or visual signals.

One form of biofeedback therapy particularly relevant to musculoskeletal pain and tension-type headaches is electromyographic (EMG) biofeedback. Patients are provided with information fed back to them from the physiologic recordings and taught to manipulate the tension in specific muscles related to their symptoms. Patients with migraines are provided with thermal feedback. They are instructed to warm the temperature of their hands by using visual or auditory cues.[37] Alternatively, patients may be given biofeedback to regulate the autonomic nervous functions via heart rate variability, which has been shown to impact pain perception.[93,94]

An innovative approach to biofeedback uses real-time fMRI ("neurofeedback") to help train people to control activation in the rostral anterior cingulate cortex (rACC) and has shown promising results. This brain region is reputedly involved in pain perception and regulation. When the participants deliberately induced changes in the rACC, there was a corresponding change in their perception of the pain.[95] However, a recent systematic review on the effect of "neurofeedback" on chronic pain points out that the promising outcomes are largely from low-quality studies and suggests that the conclusions need to wait for high-quality research on the topic.[96]

The actual mechanisms involved in the success of biofeedback are still unknown. However, with biofeedback treatment, it is assumed that the level of pain is maintained or exacerbated by dysregulation of the autonomic nervous system, which is believed to be associated with the production of nociceptive stimulation (e.g. muscle tension localized in the erector spinae in a person with low back pain). Besides the physiologic changes accompanying biofeedback, patients are provided with a sense of control over their bodies. Given the high levels of helplessness observed in those with chronic pain problems, the perception of control may be as important as the actual physiologic changes observed. A general sense of relaxation is also an important feature of biofeedback. Again, it is not clear whether the alterations in specific physiologic parameters putatively associated with pain are the most important component of biofeedback or whether it is the broader relaxation and self-control created.

Guided Imagery

Guided imagery can be useful as an adjunct to help people with pain relax, achieve a sense of control, and distract themselves away from noxious sensations, emotional distress, and demoralizing thoughts by directing their attentional focus on more positive images and sensations. A coping strategy that they can use and thereby combat feelings of helplessness.

This modality involves the generation of mental images by oneself or through the guidance of a clinician. Training usually starts with neutral imagery, such as visualizing a room in their house in their mind and progressing to more engaging and positive ones. The most successful imagery involves all the senses (i.e. vision, sound, touch, smell, and taste) as if the person is "present" within the imaged scene.

Once the person feels comfortable using the experiential imagery, a clinician and the person collaboratively work to define specific imagery or storyline that can be therapeutic for the person. When the person with chronic pain is feeling pain or is experiencing an exacerbation of pain, he or she can use imagery to help redirect attention away from the pain and achieve a psychophysiologic state of relaxation with chronic pain.

The ability to elicit experiential imagery varies across individuals, and not all people are successful in using this technique. If a person has difficulty generating a particularly vivid visual image, it may help to listen to a taped description or look at a poster or picture in a magazine on which they can focus their attention as a way of assisting their imagination.

Although some have advocated using guided imagery as a stand-alone intervention to reduce presurgical anxiety and postsurgical pain and accelerate healing,[97] it is a single modality that is most often used with other treatment interventions, such as CBT, meditation, or relaxation.[35,38]

Hypnosis

Hypnosis has been used as a treatment intervention for pain control since at least the 1850s. Hypnotic suggestions have been used to instill positive attitudes in people, facilitate compliance with treatment, foster distraction from negative thoughts or stimuli, alleviate anxiety related to medical procedures, reduce reliance on medication, and promote relaxation and rehearsal of adaptive behavior.[98]

Hypnosis has been defined as a "natural state of aroused attentive focal concentration coupled with a relative suspension of peripheral awareness." There are three central components of a hypnotic trance: (1) absorption, or intense involvement in the central object of concentration; (2) dissociation, in which experiences that would commonly be felt consciously occur outside of conscious awareness (i.e. the converse of meditation); and (3) suggestibility, in which persons are more likely to accept outside input without cognitive censorship or criticism.[99]

Hypnosis has been shown to be somewhat beneficial in relieving pain in selective people with headaches, burn injury, arthritis, cancer, and chronic back pain.[98,100,101] A meta-analysis has suggested an overall benefit of the addition of hypnosis to nonhypnotic pain management strategies, although this may be affected by the level of hypnotic suggestibility of any individual patient.[98] There are discrepancies in the literature regarding the methods used to induce hypnosis, making it difficult to accurately evaluate the efficacy of this intervention.[102] Finally, based on systematic reviews, Patterson and Jensen suggested that hypnosis has more usefulness for the treatment of acute pain than chronic pain.[100,101] Thus the degree to which hypnosis is helpful beyond the effectiveness of other interventions and for which populations it is useful and for whom remains to be elucidated.

Conclusions

A person experiencing chronic pain is continually in quest of relief that may remain elusive, which leads to feelings of helplessness, hopelessness, demoralization, and outright depression. Emotional distress may be attributed to various factors, including inadequate or maladaptive coping resources, iatrogenic complications, overuse or medications, disability, financial difficulties, litigation, disruption of usual activities, inadequate social support, and sleep disturbance. Thus chronic pain represents a demoralizing situation; the individual with pain not only faces the stress created by pain but experiences a cascade of ongoing stressors that compromise all aspects of life. Living with chronic pain requires considerable emotional resilience, tends to deplete emotional reserve, and taxes not only the person experiencing pain but also the capability of family members and significant others to provide support. Given the complexity of chronic pain experience, it should be abundantly clear that the treatment of people with chronic pain must reach beyond neurophysiology. As discussed in this chapter, a large body of evidence has demonstrated that psychological factors are critical determinants of how people with chronic pain fare. Psychological interventions are becoming standard practice in pain medicine, most commonly in conjunction with other treatment modalities. The main goals of psychological treatments are to modify the pain modulation by addressing cognitive, behavioral, and emotional factors relevant to pain and improving adaptation to the chronic state of pain and functional limitation.

Typically, psychological interventions have been provided to patients in the clinicians' office in a face-to-face situation. However, a growing body of literature demonstrates the potential of technology-delivered psychological treatments for various chronic pain conditions.[103] These approaches have the advantage of convenience to patients, availability, and potentially lower cost. Although appealing, the preliminary reports have mainly been small scale demonstration projects, not conducted in randomized clinical trials and often with no control groups, high drop-outs, and limited follow up. Although these efforts look promising, they remain in need of well-designed research to demonstrate effectiveness compared to alternatives and sustained benefits.

It is important to emphasize once again that none of the treatments described in this chapter are successful in eliminating pain completely, nor, as we noted, are they designed for this purpose. Instead, the goals are functional improvement and improved health-related quality of life. The limited success of psychological treatments on pain reduction per se is true for all modalities in pain medicine, including pharmacologic, medical, and interventional treatments. The results for all are modest.[3] Therefore most people with chronic pain have to eventually adapt to the presence of pain, learn to self-manage the symptoms, and find ways to function and stay productive despite some symptoms. Treatment modalities rooted in biopsychosocial perspectives, such as described in this chapter in conjunction with traditional, physically-based interventions, appear to be optimal treatment plans for patients with chronic pain.

It is also important to acknowledge that none of the psychological treatments described have proven effective for all individuals.[49] Currently, few data are available that consistently identify the characteristics of those who would most likely benefit from the pain treatment methods described in this chapter. It may be that psychological treatments are most effective when matched to specific patient characteristics. Research is needed to determine which treatments and how they should be delivered are most effective for patients with certain characteristics and result in the fewest iatrogenic complications and adverse events.[35,49] Positive results will permit more clinically effective and cost-effective ways to treat the difficult population of patients with chronic pain. Research is needed to test this hypothesis and identify the characteristics most likely to benefit from specific psychological approaches and treatment modalities.[104] Given the evidence reviewed, it is highly recommended that clinicians consider using psychological interventions in conjunction with medical or procedural practice in pain medicine as a comprehensive treatment program.

Key Points

- Pain is a complex, subjective experience with psychosocial, behavioral, and biologic contributors.
- The biologic treatments currently available may not be adequate, and significant levels of pain persist despite the most advanced pharmaceutical, anesthetic, and surgical treatments.
- Persistent pain affects all aspects of individuals' lives.
- People with chronic pain are demoralized because their bodies and the healthcare system have let them down.
- Chronic pain affects not only patients but also their significant others, healthcare providers, employers, and third-party payers.
- There is vast individual variation in the experience of chronic pain, styles of coping and adaptation, and response to treatment.
- Environmental factors (e.g. attention by significant others, including healthcare providers) can reinforce behavioral responses by patients.
- Patients' beliefs, attitudes, and expectations influence the experience of pain, disability, and treatment response.
- A comprehensive approach to the assessment of patients with chronic pain that addresses the medical, psychological, and environmental contributors is necessary to develop an optimal treatment plan.
- Most commonly practiced psychological approaches combine multiple techniques and skill training, as in CBT, ACT, and MBSR techniques.
- Since there is no cure for chronic pain, patients need to learn to accept their role in self-management of their pain and their lives.
- Several behavioral (e.g. relaxation, biofeedback) and cognitive (e.g. problem solving, meditation) modalities that may be helpful to patients can be taught and learned as complements to traditional medical treatments.
- Interdisciplinary pain rehabilitation programs that integrate psychological and physical treatments have been demonstrated to benefit patients with recalcitrant chronic pain.
- Research is needed to identify the best treatment combination for patients with different physical and psychosocial characteristics.

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Evidence-Based Rehabilitation Approaches to Acute and Chronic Pain Management

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A rehabilitation approach utilizes a combination of person-centered, non-pharmacologic, and pharmacologic strategies for pain management. A number of different healthcare practitioners participate and can provide rehabilitation to the patient, including physicians who specialize in physical medicine and rehabilitation, pain medicine, sports medicine, and clinicians in physical therapy, occupational therapy, and integrative health. Rehabilitation for a person with pain is used to provide treatment during the acute, sub-acute, or chronic phases and aims to reduce functional improvement and pain reduction. Rehabilitation is best approached using a multi-disciplinary team approach. While both pharmacologic and non-pharmacologic strategies are used in rehabilitation, the focus of this chapter will be on the use of non-pharmacologic strategies.

Rehabilitation Approach

A rehabilitation approach is a multi-faceted, multimodal approach to pain management with the goal of client independence in self-management.[1] The approach is based on a biopsychosocial model for pain prevention, assessment, and intervention to address the multidimensional aspects of pain and provide a personalized approach to pain management (see Figure 59.1A). The goal of the self-management program is to enhance the ability of a person to self-manage their pain through the use of physical activity, pacing, and non-drug therapies. Successful self-management requires the client to develop a mastery of transferable skills and strategies into a comprehensive self-management plan. The plan may include many aspects of pain management, such as education, movement, physical activity, and adjunctive non-pharmacologic strategies.

Multiple guidelines have been published to assist healthcare providers in developing person-centered self-management plans for the treatment of pain for a variety of painful conditions.[2–5] These guidelines routinely include exercise recommendations with strong evidence.[6–11] A recent review of guidelines for non-specific low back pain reviewing 15 different guidelines for care suggests a consistent agreement in the approaches with few discrepancies in practice guidelines.[2–4,8,12–18] Bed rest is avoided for all stages of injury, and education, psychosocial interventions, and exercise are particularly recommended for chronic pain.[16]

The release of the Institute of Medicine (IOM) Report in 2011, Relieving Pain in America, recommended the use of a comprehensive, interdisciplinary approach as the most effective way to treat pain.[19] In addition, the Department of Health and Human Services National Pain Strategy in 2016 emphasized self-management approaches for the management of chronic pain as well as prevention strategies for acute and chronic pain.[20] The National Pain Strategy also recommended the use of self-management programs.[20]

The National Pain Strategy (United States) recommends that "people experiencing pain would have timely access to patient-centered care that meets their biopsychosocial needs and takes into account individual preferences, risks, and social contexts."[20] The use of a biopsychosocial approach by the clinician entails a comprehensive assessment of individuals with chronic pain to develop an integrated, patient-centered plan of care using evidence based practices. While most individuals are managed through primary care providers, referral to an interdisciplinary team should be used when needed. Therefore treatment is often multi-disciplinary and aims to alleviate pain and improve the client's physical function and psychological health.

Ideally, rehabilitation team approaches involve multiple practitioners and can be multi-disciplinary or interdisciplinary. The approach used will likely depend on the current status of the individual with pain, geographic location, access to care, and client resources.[21] Multi-disciplinary treatment, defined as a multimodal treatment provided by practitioners from different disciplines,[21] is the most common and generally involves each profession working separately with discipline-specific therapeutic goals. On the other hand, interdisciplinary treatment, defined as multimodal treatment provided by a multi-disciplinary team collaborating in assessment and intervention using a shared biopsychosocial model and shared goals,[22] is often used when unimodal treatment is insufficient.

An interdisciplinary team will vary in size and depend on the needs of the individual. Interdisciplinary team members begin with an individual or a person with pain. Physicians, physical therapists, psychologists, or psychiatrists make up the remainder of the team.[23] Additional team members may comprise professionals from occupational therapy, pharmacy, dietetics, and complementary and integrative health fields. A key aspect of an interdisciplinary team is regular communication and meetings

between team members and between the patient and team. A physician provides comprehensive examination and assessment of pain and clinical presentation, coordinates care for the individual, and provides both pharmacologic and non-pharmacologic strategies for pain relief. Physical therapy pain management focuses on improving function and movement through education, exercise, and electrophysical agents.[24–26] Occupational therapists assist individuals' participation in daily activities through the adaptation of activities, self-management, education, and exercise. Psychologists provide skills for individuals with pain to cope with emotions, feelings, and behavior related to pain, using various approaches to assist in self-management related to pain beliefs.[27,28] Pharmacists provide services through education and management of medications, including dosage, monitoring adverse responses to medication, costs, and decision making, to both individuals with pain and with prescribing providers.[29,30] Other professionals who may be part of the rehabilitation team may include care in diet, chiropractic, acupuncture, massage therapy, music therapy, recreational therapy, and vocational therapy, to name a few. Each interdisciplinary team will be unique to the individual and focus on the inclusion of professions and strategies to best meet the needs of the individual (Table 59.1).

Approach to Treatment

In a rehabilitation approach to pain, a hierarchy of care is used to treat pain. Acute pain treatment is designed to determine and treat the underlying cause, maintain or improve function, and reduce pain. Chronic pain treatment is designed to promote self-management and improve function and quality of life. Adequate treatment of pain and risk factors during an acute episode of pain is essential to decrease the potential for transition to chronic pain.[31–33]

Based on pain presentation, patient preference, clinical experience, and clinical evidence, various approaches can be used in rehabilitation. The primary interventions in rehabilitation are education and exercise. Secondary interventions can include the use of electrophysical agents,[34] manual therapy,[5,35] and pharmacology.

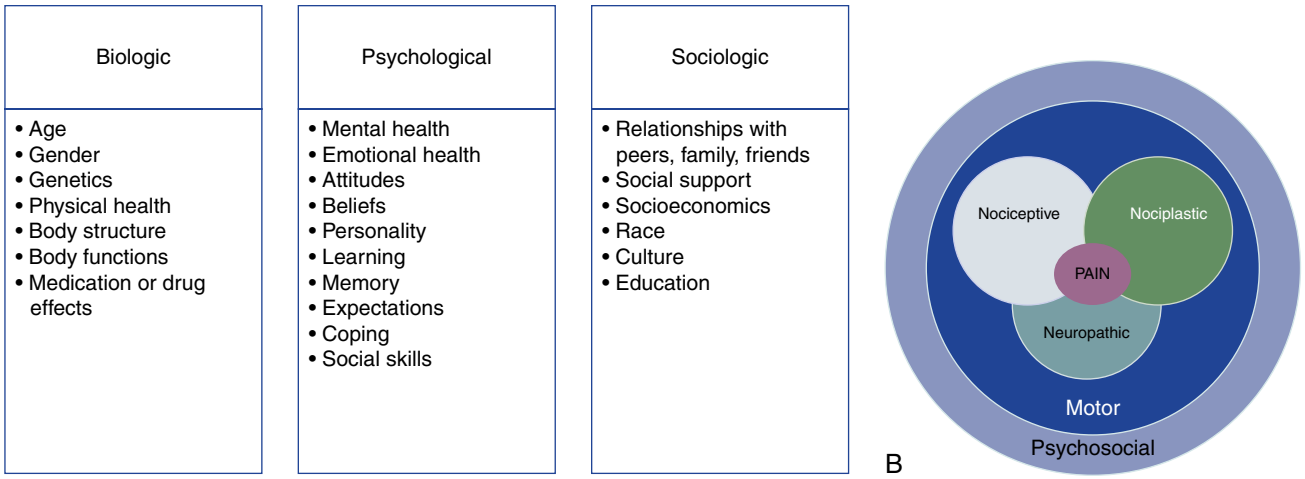
Pain Management Considerations

Evaluation

Key aspects of the evaluation for rehabilitation focus on function, biomechanical presentation, and activities of daily living at home and work. Movement can be impacted by pain, and

TABLE 59.1 Roles of Professionals in Rehabilitation Approach to Pain Management

Profession	Role
Physician	A medical provider or physician provides comprehensive examination and assessment of pain and clinical presentation with a specialty in musculoskeletal conditions. A physician may utilize pharmacologic and non-pharmacologic strategies for pain relief for acute to chronic pain. A medical provider assists in coordinating care through the interdisciplinary team, and a pain management specialist may provide interventional pain management procedures.[1]
Nursing	Nursing pain management includes both pharmacologic and non-pharmacologic strategies. Nursing pharmacologic strategies include monitoring analgesic therapy, medication reconciliation, medication education, and safety. Non-pharmacologic strategies in nursing include client education regarding pain and pain management, relaxation, distraction, and assisting in the referral process for the interdisciplinary team.[2]
Physical Therapy	Physical therapy pain management focuses on improving function and movement through education, exercise, electrical stimulation, heat and cold modalities, motor imagery, sensory re-education, and virtual reality.[3,4]
Occupational Therapy	Occupational therapists assist individuals with pain to participate in daily activities through adaptation of activities, self-management, education, and exercise. The occupational therapist will also include interventions for relaxation, stress management, pacing, problem solving, and communication skills training.[5]
Psychology	Psychologists help individuals and caregivers cope with emotions, feelings, and behavior related to pain, most often chronic pain. They have a wide variety of approaches to assist in self-management related to pain beliefs (self-efficacy, catastrophizing, coping fear and avoidance, life control acceptance and psychological flexibility, sleep, negative affect, cognition, quality of life, relaxation, biofeedback, cognitive behavior approaches to pain self-management).[6,7]
Pharmacy	Pharmacists have an integral role in the pain self-management process. They provide services through and between the stages of pain–acute, subacute, and chronic. They provide education to individuals with pain regarding medication information, use, dosage, monitoring, and possible adverse responses to medication, costs, and decision making to both individuals with pain and with prescribing providers (ref- us pharmacist resource). As part of the interdisciplinary pain management team, pharmacists collaborate for medication reconciliation, the timing of medication if needed for interventions, and possible adverse responses to medication.[8]
Dietitian	Dietitians play an important part of the interdisciplinary team for the individual with pain. Nutrition plays a large part in how the body responds to increased inflammation and pain. A dietitian assesses an individual's diet and nutritional status, caloric intake, hydration, and medical and nutritional needs. They provide education for food planning that may include anti-inflammatory foods, whole foods, and nutrients to assist in the self-management of pain. Studies looking at the influence of diet on inflammatory markers show that consumption of foods high in fiber, healthful oils, fruits, vegetables, and those low in sugars, starchy carbohydrates, and unhealthful fats can reduce inflammation and disease. The dietitian includes the biopsychosocial aspects of diet and nutrition in a person-centered approach.[9]
Other	Other professionals of the interdisciplinary team may include caregivers in chiropractic, acupuncture, massage therapy, music therapy, recreational therapy, and vocational therapy, to name a few. Each interdisciplinary team will be unique to the individual and focus on the inclusion of professions and strategies to meet the needs of the individual best.[9]



• **Figure 59.1 A,** Biopsychosocial factors to consider in pain management. **B,** Biopsychosocial Model: Adapted from Chimenti RL, et al. (2018).[1]

altered movement patterns can impact pain (see Figure 59.1).[36,37] Rehabilitation specialists focus on the International Classification of Functioning (ICF) from the World Health Organization to determine functional limitations and activity participation.[38] Performance-based functional tests, such as a walk test or sit-to-stand test, evaluate the ability of a person to perform a standardized task. Biomechanical assessments include posture, strength, and range of motion of the affected body structures. Further impact of pain on function and ability to perform activities of daily living at home and work are used to guide treatment.[39,40]

Assessment of psychosocial variables is critical in the evaluation process to determine the impact of psychosocial variables on function and pain. Each individual has a range of factors with dynamic interactions between biologic, sociologic, and psychological factors that modulate the pain experience and are unique to each person.[41,42] Psychological factors can enhance pain and impact recovery from pain.[41] Both positive and negative psychosocial factors influence the response to pain. Negative factors can include increased pain catastrophizing, fear avoidance, fear of pain, fear of movement, negative affect, and decreased mood. Positive factors include enhanced resiliency, self-efficacy for managing pain, pain-related coping, and self-management skills.[41,43,44]

The three mechanisms of pain are useful for guiding treatment. Nociceptive pain arises from actual or threatened damage to non-neural tissue and is caused by the activation of nociceptors in a normally functioning somatosensory system.[45] Nociplastic pain arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing pain.[45] Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system.[45] These mechanisms can overlap in individuals with acute or chronic pain. Identifying the mechanism of pain can help guide evidence based evaluation and interventions that are person-centered (Figure 59.1).[36,37]

Development of a Plan of Care

Based on the evaluation results, along with patient and clinician preferences, a variety of approaches can be used to manage pain from a rehabilitation perspective. The primary goal for pain management using a rehabilitation approach is to enable individuals to develop independence in the self-management of pain. It is important to regularly assess the strategies that are working and those that are not, develop new strategies that may be more successful or add additional tools to go in the individual's self-management "toolbox." This independent self-management plan allows the person with pain to play an active role in setting goals for pain relief, reduction, function, activities, and participation at home or in the community. This skill development should be individualized and focus on problem solving, patient-centered goals, and communication within and between disciplines. Tools for self-management include education, functional training, self-care, home and/or work management, therapeutic exercise, manual therapy, and electrophysical agents.[46–48] A combination of interventions is important to focus on person-centered care and provide multiple strategies to manage pain. While each of these interventions alone may have success, a combination of these interventions is more effective than one intervention alone.[35,49]

One common denominator in all these interventions is education and the utilization of an evidence based approach to active engagement and participation of the client. Education is critical for the independence of self-management. Determining a patient's learning style, preferences, previous experience, and expectations is the first step to promoting independence and future adherence to the tools needed for self-management of pain.

Specific Rehabilitation Interventions

Self-Management Strategies

Self-management strategies are the standard of care for individuals with either acute or chronic pain.[50,51] For those with chronic disease, self-management programs encourage active participation and support ongoing medical care.[46–48] Healthcare practitioners should adopt approaches that allow patients to be active during the recovery process. All interventions (exercise, manual therapy, biophysical and electrical agents, and behavioral modification) should be delivered with an education component stressing self-management and client adherence.

For patients with acute pain, the importance of activity modification (positions of comfort and avoidance, appropriate movement) and education on the expected course of pain are the primary interventions.[52–54] Secondary management strategies of electrophysical agents can be employed for home management of pain or supplement pharmacologic interventions.[16,55–57] Postoperative patients may benefit from guided imagery, relaxation therapy, or music/video distraction pain management.[58] As the acute phase progresses, the focus is directed to the addition of appropriate

exercise, activity, and functional activities to maintain and improve function.[59] Education is progressed to understanding "hurt" versus "harm" and the addition of exercise/movement designed to stress tissues for optimal healing.[60,61] Electrophysical agents may be employed to assist in participation in exercise interventions.[36,56,62,63]

Self-management has become increasingly important and has become the main goal for people to manage their chronic pain effectively.[1,64] Common components of self-management for chronic pain include 1) education on pain and disease, 2) education on increased activity and pacing, 3) development of pain management skills using non-pharmacologic approaches, and 4) development of coping skills.[65–67] Self-management programs can be delivered in many formats, including individualized, group classes, or internet-based, and are often provided by multiple practitioners on the rehabilitation team.[67–70] Self-management for this population can be difficult. Therefore methods for developing adherence to the intervention become the most critical.

The main goal of self-management is to provide resources and skills to the client to manage their chronic pain effectively.[61,67] Self-management is part of a more comprehensive plan that includes physical therapy, medical management, and psychological interventions, as appropriate.[22,71] The aim is to make the client an active participant in managing their condition; thus the primary outcome expected is a change in behavior.[72] The development of an individualized skill set, or toolbox, is a key component of all self-management programs. This toolbox may include pacing, relaxation and stress management, physical activity and exercise, and safe and effective pain-relieving modalities (transcutaneous electrical nerve stimulation [TENS], heat, cold).[56,73–77]

Clinical data practice guidelines and the National Pain Strategy (United States) recommend the use of self-management skills for the management of a variety of chronic pain conditions.[12,71,78,79] Systematic reviews on the effectiveness of self-management programs are mixed and show small effect sizes when given alone.[68,80–84] The key components of self-management programs are still being developed. More recent studies using a biopsychosocial and individualized approach as an adjunct to the standard of care have shown that self-management programs improve adherence to exercise and physical therapy.[85–88]

Physical Activity and Exercise

Exercise is a key component of the rehabilitation approach. Clinical practice guidelines strongly recommend exercise for various painful conditions,[12,16,89–94] and exercise is supported by systematic reviews of the literature suggesting exercise is a first line treatment for individuals with chronic pain.[95] Mechanistically, exercise is a multimodal treatment with peripheral effects at the injury site to promote healing and pain relief, reduce central excitability, increase central inhibition, modulate the immune system, and modulate mood.[96,97] Several neurotransmitters and receptors are activated by exercise, including endogenous opioids, serotonin, and cannabinoid receptors.[96,97] Additionally, exercise can improve motor control, strength, aerobic capacity, and function.

Movement therapies, including traditional structured exercise (aerobic, strengthening), functional training, complimentary exercise techniques (yoga, tai-chi), and behavioral exercise approaches (graded exercise), can be used to reduce pain and disability, improve function, prevent the development of chronic pain, and reduce the recurrence of chronic pain (for review see reference 95). While clinical evidence suggests that exercise training is effective for most pain conditions, the type of exercise may be less important than the act of doing exercise. Several studies have compared different types of exercise for different types of pain and showed no difference between active exercise interventions.[98–101] For example, a comparison of proprioceptive training to craniocervical flexion in individuals with neck pain exercises showed no differences between groups.[99] Similarly, a comparison of graded exercise and graded exposure for those with chronic low back pain showed similar effects.[102] We suggest that this lack of specificity of exercise may be related to the multiple and widespread mechanisms by which exercise reduces pain and improves function. Thus the most important component of exercise selection is choosing a mode that the person will adhere to and enjoy.

Adherence is critical to the success of an exercise program.[103] High levels of self-efficacy, self-motivation, intention to engage, social support, and health locus of control have been associated with improved adherence to interventions, including exercise.[72,85,104–106] Assessing these variables and using strategies aimed at increasing motivation and some level of supervision by the clinician may also significantly improve adherence.[107] Shared decision making is a component of improving adherence. Frameworks designed to include patients in the decision making process and that are tailored to the individual and their diagnosis may improve adherence.[3,85,104] As noted above, self-management programs can improve adherence to exercise,[72,85–87,107,108] and these should be employed together to achieve the best outcomes. With the importance of adherence emerging, developing measures that capture this outcome in pain populations is warranted.[104,109]

Manual Therapy

For the purpose of this chapter, manual therapy techniques are defined as the skilled hand movements of clinicians intended to improve tissue extensibility, modulate pain, promote relaxation, and mobilize soft tissue and joints.[59] There are numerous methods whereby clinicians use their hands, such as classical massage, soft tissue mobilization, and joint manipulation. The use of massage therapies has been documented across the ages, and nearly every society and culture has a form of manual therapy in its history. Massage may have therapeutic effects indirectly through reductions in inflammation, promotion of healing, and restoration of normal movement patterns.[110–112] While clinical evidence for massage therapy exists, the evidence is generally weak and based on lower quality clinical trials. Furthermore, massage is rarely used as a standalone treatment, potentially creating bias in reports attempting to evaluate the overall effectiveness of massage when evaluated in isolation. This concept is illustrated by a systematic review including 23 studies addressing neck pain, where the main finding was that pain reduction with the combination of manual therapy and exercise was better than manual therapy or exercise alone.[113] Systematic reviews examining the effectiveness of massage have reported significant reduction in pain and improvements in function compared to sham in patients with low back pain, fibromyalgia, and neck pain.[114–117] However, massage produces similar improvements in pain and function compared to other therapies, and only short term use is suggested.[118] The reviews note the lack of consistency in reporting specific techniques and low quality methodology, making clinical recommendations unclear. Interestingly, two clinical trials examined the duration of massage, and both showed that durations of 60 min over several weeks were more effective than 30 min duration in individuals with either knee osteoarthritis or neck pain.[119,120] Furthermore, in individuals with non-specific low back pain, similar results were found using either traditional massage

techniques or targeted soft tissue techniques.[121] Thus systematic reviews and clinical trials support the effectiveness of massage when administered repetitively for short term pain relief.

Manipulation includes both high velocity, short duration joint movements as well as low velocity, longer duration joint movements (also referred to as joint mobilization). Traditionally, joint manipulation has been used to improve the movement of the restricted joints. However, evidence suggests that joint manipulation modulates nociceptive transmission both peripherally and centrally. Peripheral nociception can alter motor neuron excitability and muscle spindle activity and reduce electromyography (EMG) activity of paraspinal muscle.[122–125] Joint mobilization can also increase pain thresholds, reduce central excitability measured by temporal summation, and produce analgesia through the release of noradrenaline and serotonin in the spinal cord.[122,125,126] Other neurotransmitters may also be involved in analgesia, including μ-opioid receptors peripherally, adenosine receptors both peripherally and centrally, and cannabinoid receptors both peripherally and centrally.[127,128] Thus these data suggest that joint manipulation modulates the motor activity and activates endogenous inhibition peripherally and centrally to reduce pain.

Systematic reviews of joint manipulation routinely show statistically significant effects on pain reduction in patients with neck or low back pain.[92,94,129–132] It should be noted that these effects are short term and may not be clinically significant, with an effect less than 10 on a 100-point pain scale. Spinal manipulation is more effective than sham but shows similar analgesic effects to other adjunctive therapies, including physical therapy or exercise.[132] Furthermore, for those with acute low back pain, spinal manipulation is not more effective than control conditions.[131] Joint manipulations and mobilizations can also be applied to peripheral joints to improve the range of motion and function and reduce pain. Few studies have examined the peripheral joint manipulation. In people with osteoarthritis, lateral epicondylalgia, or acute or chronic ankle sprains, joint mobilization reduces pain and improves function compared to placebo.[126,133–135] Thus joint mobilization can provide short-term pain relief and improve function.

Biophysical and Electrotherapy Agents

Biophysical and electrotherapeutic agents are commonly used as adjunct treatments to self-management and exercise programs to reduce pain and promote healing.[56] These treatments include the use of heat, cold, and electrotherapy. These modalities are safe, inexpensive, and can be performed in home environments. A review of the evidence of these adjunctive interventions (Table 59.2) suggests that attention to proper dosing is critical to their effectiveness.[56] For example, electrotherapy treatments delivered at a sensory threshold[34] or ultrasound treatments passing over a large area with a short treatment duration are ineffective in reducing pain.[136] Thus when applied at adequate doses, biophysical and electrotherapeutic agents can be included as part of a pain management program.

Electrotherapy. For the purpose of this review, the term electrotherapy represents any form of electrical current applied to the body to reduce pain. The most frequently utilized clinical approaches include TENS and interferential current (IFC). TENS is the application of a low voltage pulsed alternating current via electrodes applied to the skin. Importance parameters include the application of high, low, or mixed frequency current; a sufficient amplitude to evoke a strong but comfortable sensation; and a duration of at least 30 min. IFC is the application of two high frequency currents applied to the skin via four electrodes to produce an amplitude-modulated beat frequency in the tissues.

TABLE 59.2 Summary of Effectiveness of Non-pharmacologic Approaches to Pain Management

Condition	Self-management	Exercise	TENS/IFC	Heat	Cold	Ultrasound	Massage	Joint Manipulation	Photobiomodulation
Acute Low Back Pain	#/+	#	#	#	#	-	#	#	-
Chronic Low Back Pain	+	+	#	+	#	-	#	+	-
Chronic Knee Pain	+	+	+	-	-	+	-	-	+
Chronic Neck Pain	+	+	#	#	#	#	+	+	-
Fibromyalgia	+	+	+	#	#	-	+	#	+
Osteoarthritis	+	+	+	+	+	#	#	-	+
Rheumatoid Arthritis	+	+	+	+	+	+	#	-	-
Peripheral Neuropathy	+	+	+	-	-	-	-	-	#
Postoperative Pain	+	+	+	#	#	-	#	-	-

+, Evidence based on systematic reviews or clinical practice guidelines. #, inconclusive/equivocal evidence from systematic reviews or clinical practice guidelines; - , lacking evidence; *IFC*, interferential current; *TENS*, transcutaneous electrical nerve stimulation.

Inconclusive/equivocal evidence from systematic reviews or clinical practice guidelines

- Lacking evidence

TENS and IFC stimulate the afferent fibers in the skin and, more importantly, the deeper tissues.[137] TENS analgesia is produced by the activation of neural pathways in the central nervous system by reducing central excitability and increasing central inhibition (for an extensive review of the mechanisms, see reference 37). Briefly, high frequency stimulation (50–125 Hz) activates δ-opioid receptors, and low frequency TENS (1–10 Hz) activates μ-opioid receptors throughout the central nervous system pathways involved in analgesia.[34,138] TENS reduces central excitability by reducing central sensitization of dorsal horn neurons and the release of the excitatory neurotransmitter glutamate in the dorsal horn. TENS also produces analgesia through the activation of serotonin, γ-aminobutyric acid (GABA), and muscarinic receptors spinally.[34,37,139,140] Thus TENS uses multiple mechanisms to produce analgesia.

Clinically, TENS is used for both acute and chronic pain. Several systematic reviews have reported negative or inconclusive findings regarding the use of TENS for a variety of pain conditions, including osteoarthritis, postoperative pain, and fibromyalgia.[141–146] On the contrary, reduction in pain has been reported for diabetic peripheral neuropathy, postoperative knee arthroplasty, fibromyalgia, post-thoracic surgery, and rheumatoid arthritis.[147–152] Furthermore, a systematic review and meta-analysis on chronic pain similarly reported a significant reduction in pain when compared to a placebo.[153]

Two recent analyses of the TENS literature suggest several issues in the quality and design of existing TENS trials that lead to equivocal results.[154,155] One key aspect of TENS effectiveness is the provision of an adequate dose of stimulation with a minimal intensity that is strong but comfortable.[154,156] This is supported by systematic reviews that show that when applied at adequate doses, TENS is effective for postoperative pain, knee osteoarthritis, and acute pain.[157–159] Another issue related to existing clinical trials is the timing of the outcome measurement, as TENS works best while the TENS unit is turned on.[77,159] This is not surprising given the neuropharmacologic mechanisms of TENS (reviewed above). Furthermore, in both human and animal studies, repetitive TENS administered at the same frequency can lead to analgesic tolerance, and low frequency TENS is less effective in opioid-tolerant individuals.[160–163] Tolerance effects are because of tolerance at spinal opioid receptors[160] and can be alleviated by alternating between low and high frequency in a single session.[164] A recent clinical study testing the efficacy of TENS in fibromyalgia addressed the weaknesses of prior studies using an alternating frequency of stimulation, strong but comfortable intensity, and measured the effects of TENS with the unit on.[63] This study showed a clinically significant reduction in movement-evoked pain and fatigue, as well as resting pain and fatigue when compared to placebo or the no-TENS condition. The number needed to treat was relatively low (three to four), while the number needed to harm for minimal adverse events was high (20–100),[63,165] indicating that TENS is effective and safe. A responder analysis showed that the response to a single treatment predicted the response to treatment one month later, with those showing a 10% response to the first treatment likely to respond with greater than 30% reduction after a month of home use.[165] Thus TENS, when applied at adequate doses, is effective for reducing movement-evoked pain in individuals with fibromyalgia, with similar efficacy to pharmaceutical treatments. TENS is low cost and safe and is a recommended choice for individuals with both acute and chronic pain.

IFC is widely used to treat musculoskeletal pain, and systematic reviews show effectiveness for various pain conditions, including osteoarthritis, fibromyalgia, and postoperative pain.[141,166–168] In contrast, a meta-analysis by Fuentes et al. showed that IFC given alone was not more effective than placebo, manual therapy, or massage and was unclear when applied as an adjunct intervention to existing treatment.[169] Importantly, TENS and IFC produce similar effects in the treatment of acute and chronic pain.[168] The systematic reviews caution about the quality and heterogeneity of the studies.

Thermal modalities (heat and cold agents) have been used throughout history, and the concept of heat or cold-induced analgesia is generally well accepted. The process is characterized by energy transfer between the agent and tissues of the body. Moist or dry heat packs are examples of common heating agents, and cryotherapy can be accomplished with ice massage, ice bags, or commercial cold packs. Hydrotherapy can be used in clinical settings. These have the advantages of circumferential exposure, the ability to maintain a constant temperature, and the ability of the client to exercise while receiving the thermal intervention. The type of agent is selected by the clinician depending on the diagnosis, the body part in question, the stage of injury, and the ease of application if the modality is intended for client self-management of symptoms or use in a clinical setting.

The effects of thermal therapy on pain are because of both direct and indirect effects. Direct effects include changes in nociceptor firing in the peripheral tissues where the agent is applied and alterations in nerve conduction velocity.[170] Indirect effects include changes in blood flow, tissue metabolism, and removal of chemical irritants in the treatment area.[170] In the case of heat therapies, tissue extensibility and joint stiffness may be reduced, resulting in decreased input of nociception to the central nervous system. Other neural mechanisms for heat therapy propose a reduction in muscle spasm because heat reduces type II spindle afferents firing.[171]

Despite widespread use and general acceptance of pain-reducing qualities of thermal therapy, sparse clinical evidence exists to support its use. Few high quality studies have investigated the effectiveness of thermal modalities, resulting in mixed data on the effectiveness of thermal modalities for pain relief.[130,172–177] For example, Wong et al.[130] concluded that heat, cold, and ultrasound therapy are ineffective for reducing neck pain, while the American College of Physicians guidelines and a systematic review showed that heat therapy reduces low back pain.[16,176] For postoperative pain, it is not recommended or discouraged,[3] while for rheumatoid arthritis, it is recommended.[178] For osteoarthritis, cold therapy improves the range of motion, function, and knee strength but does not affect pain.[173,179] While the evidence is mixed, the use of thermal agents is low cost, easy to apply, and low risk. Heat and cold therapy can be applied at home by the subject and should be included in a self-management program as a non-pharmacologic option.

Therapeutic ultrasound is the use of acoustic sound waves applied to tissues and has been widely used for over 60 years. Treatment effects are dependent on parameter settings and include both thermal and non-thermal effects. The effect of ultrasound on pain can be attributed to the targeting of deeper tissue by improving blood flow to the area, increasing tissue metabolism, and increasing tissue extensibility.[136,170] Thus the vascular changes of improved delivery of oxygen and nutrients and removal of metabolic irritants can account for the reduction in pain with the use of ultrasound.

Parameters for treatment included treatment frequency (1 or 3 MHz), intensity (0.01–2.00 Watts/cm^2), and treatment duration. Ultrasound applied at intensities greater than 1.0 Watt/cm^2 is reported to increase tissue extensibility and decrease inflammation, and pain reduction is typically not the primary goal of clinicians using ultrasound. The clinical use of ultrasound is widely

used and remains popular despite conflicting reports and relatively low quality evidence support for this modality.

Despite its widespread use, research supporting its use for pain reduction is limited and inconclusive. Systematic reviews have shown that ultrasound does not affect pain in patients with low back pain, neck pain, carpal tunnel syndrome, rotator cuff tendinopathy, or acute ankle sprains.[130,180–184] Although several RCTs support the use of ultrasound in the treatment of myofascial pain, one systematic review of 10 studies suggests that the evidence is unclear because of the high risk of bias and low quality evidence.[185] In contrast, systematic reviews have demonstrated the efficacy of ultrasound for pain reduction and functional improvement in people with knee osteoarthritis.[186–188] Ultrasound is recommended for rheumatoid arthritis and calcific tendonitis of the shoulder.[189,190] Thus the evidence for the use of ultrasound is equivocal, except for a few very specific conditions, and the clinical utility of this modality is unclear.

Photobiomodulation. Over the last 30 years, photobiomodulation also referred to as low level laser therapy, has been used to treat painful musculoskeletal conditions. This non-pharmacologic intervention uses low energy irradiation of tissue to alter cellular processes and provide an anti-inflammatory effect.[56] Similar to other non-pharmacologic interventions, studies of photobiomodulation showed a pattern of wide variability in the results obtained. Studies that use the World Association for Laser Therapy parameters to deliver what is considered an effective dose window (wavelengths in the range of 632–1064 nm) are associated with increased effectiveness for a variety of musculoskeletal conditions.[191–193] Similarly, recent systematic reviews indicate that when properly dosed, photobiomodulation is effective for reducing pain in the management of musculoskeletal conditions, shoulder tendinopathy, knee osteoarthritis, plantar fasciitis, and fibromyalgia.[151,185,193–197] As with other non-pharmacologic interventions, reviewers suggest participant heterogeneity and trial design in the studies included warrant caution in the interpretation of results.[191] However, photobiomodulation is emerging as an effective tool for pain reduction in various painful conditions.

Emerging non-pharmacologic interventions. Three other non-pharmacologic adjunct interventions for pain management in recent years include extracorporeal shock wave therapy (ESWT), dry needling, and static magnet therapy. ESWT is a pulse of acoustic energy believed to cause localized microtrauma that stimulates angiogenesis. Recent interest in ESWT has resulted in numerous randomized controlled trials for Achilles and knee tendinopathy, lateral epicondylitis, low back pain, and other musculoskeletal pathologies. One systematic review concerning the treatment of lateral epicondylitis showed a significant reduction in pain up to six months after treatment compared to traditional ultrasound.[198] Pain reduction for plantar fasciitis showed favorable results of ESWT when compared to placebo, but the results suggest that neurostimulation, traditional ultrasound, and photobiomodulation may potentially be better alternatives.[199] A systematic review comparing ESWT to corticosteroid injection for plantar fasciitis showed that both methods decreased pain.[200] This finding is worth considering for those desirous of a noninvasive intervention. Given the large number of individual studies of ESWT and these preliminary findings, additional high quality randomized controlled trials of this modality are warranted.

Dry needling involves the insertion of a solid filiform needle into the trigger areas of the muscle. Evidence for the use of dry needling is controversial. For orofacial pain and general musculoskeletal conditions, systematic reviews have shown inconclusive results because of the heterogeneity and quality of the studies.[201–203] In contrast, for myofascial pain, a recent systematic review concluded that dry needling reduced pain when compared with placebo or no treatment, but had similar results compared to other therapeutic approaches.[204–206] The effects of dry needling are immediate and can last up to four weeks.[206] However, because of the small number of high quality randomized controlled trials, additional studies should be performed to support the use of dry needling for myofascial pain.

Static magnetic therapy involves the use of pulsed magnetic fields. Magnets have been used for therapeutic purposes for more than 2000 years.[207] Over the last 20 years, magnets have been incorporated into garments and therapy wraps. They are relatively inexpensive and worn without direct supervision, have low risk, and therefore can be included as part of a self-management strategy. However, we found no convincing evidence indicating their effectiveness in pain management.

Summary

The use of a rehabilitation approach to pain management is a patient-centered process, with the primary goal of an individual's independence in the self-management of pain. It is based on a biopsychosocial model that incorporates biologic, psychological, and sociologic factors. In this model, it is important to consider the stage of pain and inflammation, source of pain, positive and negative psychosocial factors, environment, participation, activities, and function for the individual with pain. With the goal of independence in the self-management of pain, it is important to utilize a team-based rehabilitation approach that includes the requisite disciplines, evaluation, and specific evidence based interventions to address the goals and needs of the individual in pain. Individuals in pain should be active participants in the process, which is better when delivered in a multimodal, dynamic fashion. Education is a key factor that is woven into this approach across disciplines, interventions, and strategies. All interventions (exercise, manual therapy, biophysical and electrical agents, behavioral modification) should be delivered with evidence based dosing parameters and an education component emphasizing self-management and client adherence.

Key Points

- The goal of a rehabilitation approach to pain management is self-management independence. The main goal of self-management is to provide resources and skills to clients to effectively manage their pain.
- A rehabilitation approach to pain management is patient-centered, based on a biopsychosocial model, and utilizes a multidisciplinary team as appropriate for the individual in pain.
- Evidence based guidelines and interventions should be utilized in a rehabilitation approach to pain management.
- A combination of interventions is important to focus on person-centered care and provide multiple strategies to manage pain. A combination of interventions was more effective than one intervention alone.

- Non-pharmacologic interventions of education and exercise/movement should be considered as first line treatments in all stages of pain.
- The aim of a rehabilitation approach is to make the client an active participant in managing their condition; thus the primary outcome expected is a change in behavior with a long-term goal of adherence to self-management of pain.

Suggested Readings

https://www.iprcc.nih.gov/sites/default/files/documents/NationalPainStrategy_508C.pdf. Publisher is NIH Interagency Pain Research Coordinating Committee (IPRCC).

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Physical Rehabilitation for Patients With Chronic Pain

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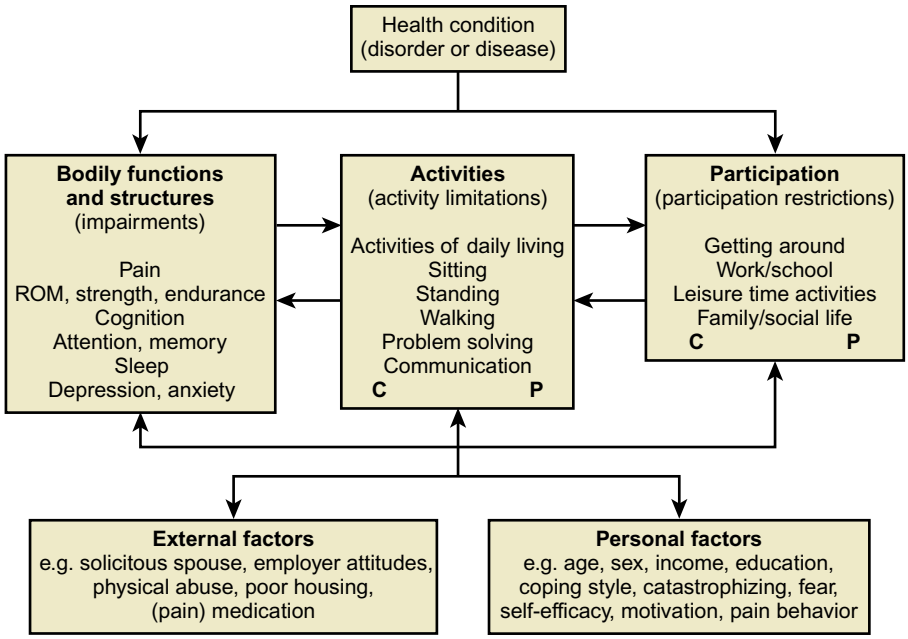
Ideally, patients with pain related disability resulting from chronic pain are treated by an interdisciplinary team of health professionals, commonly consisting of physicians, psychologists, physical and occupational therapists, social workers, and nurses, to address the biopsychosocial nature of pain. Interdisciplinary treatment is defined as multimodal treatment provided by a multi-disciplinary team collaborating in assessment and treatment using a shared biopsychosocial model and goals. For example, the prescription of an anti-depressant by a physician alongside exercise treatment from a physiotherapist, and cognitive behavior treatment by a psychologist, all working closely together with regular team meetings (face to face or online), agreement on the diagnosis, therapeutic aims, and plans for treatment and review.[1] Rehabilitation specialists working in pain management settings appreciate the complexities of chronic (vs. acute) pain, i.e. unclear relationships between pain, impairments, and disability, and the need to address the behavioral, emotional, and cognitive aspects of chronic pain. Chronic pain is understood as a disease, a pathology of the nervous system that produces abnormal changes in the brain and spinal cord and not as a symptom or warning of tissue damage.

Patients come to our pain management programs with certain expectations for evaluation and treatment. Although several studies investigated the expectations of patients with chronic pain of their physicians in a pain management program, there is a paucity of patients' expectations of their rehabilitation specialists. Most patients expected an explanation or an improved understanding of their pain problem (pain education), pain relief, and a definitive diagnosis from physicians.[2,3] Many patients with chronic pain resist referral to physical rehabilitation. Part of the difficulty lies in the history of treatment failures with which patients often present. Several factors may be responsible for past treatment failures, including persistent failure of health professionals (physicians, physical and occupational therapists) to recognize and treat the differences between acute and chronic pain states, past treatment that did not address the emotional and cognitive aspects of chronic pain, and an inability of the patient to recognize anything less than total pain relief as success.[4] Therefore it is crucial to identify patient expectations at the initial visit to prevent disappointment with referrals to physical rehabilitation for pain management.

Patient Evaluation

In evidence based practice, clinical decisions must include consideration of, first, the patient's clinical and physical circumstances to establish what is "wrong" and what treatment options are available to address this problem. Second, the latter needs to be tempered by research evidence concerning the treatment options' efficacy, effectiveness, and efficiency. Third, given the likely consequences associated with each option, the clinician must consider the patient's preferences and likely actions (in terms of what interventions she or he is ready and able to accept). Clinical expertise is needed to bring these considerations together and recommend a treatment that the patient agrees to accept.[5] The purposes of a rehabilitation specialist evaluation are to establish a baseline from which to plan and begin interventions, help to select appropriate interventions, and evaluate the efficacy of interventions.

As described in the biopsychosocial model of pain introduced by Fordyce, contributing factors to disability can be biologic, psychological, as well as social.[6] Essential in this model is the idea that factors maintaining the pain problem are not necessarily the same as those initiating pain. Therefore to establish a baseline, a thorough inventory of all factors contributing to a patient's perceived level of disability is important. The International Classification of Functioning, Disability and Health (ICF) provides a biopsychosocial model that identifies three concepts described from the perspective of body systems, the individual, and society. Within the context of health, the ICF defined *bodily functions and structures* as physiologic functions of body systems or anatomic elements, such as organs, limbs, and their components. Second, *activity* is defined as the execution of specific tasks or actions by an individual, whereas *participation* is envisioned as encompassing involvement in a life situation. In the ICF, *functioning* refers to all body functions, activities, and participation. *Disability* is the ICF umbrella term for impairment, activity limitation, and participation restrictions. Contextual factors are provided within the ICF framework (Fig. 60.1), consisting of external environmental factors (such as significant others, employers, medications, and healthcare providers) and personal factors (such as age, education, income, worry that activity will exacerbate pain or injury resulting in avoidance of activity to prevent anticipated negative consequences).



• **Figure 60.1** Example of International Classification of Functioning, Disability, and Health (ICF) framework. *C*, Capacity; *P*, performance; *ROM*, range of motion. (Adapted from Ustun TB, Chatterji S, Bickenbach J, et al. The international classification of functioning, disability and health: a new tool for understanding disability and health. *Disabil Rehabil.* 2003;25:565–71.)

Qualifiers for the activities and participation classification make it possible to clearly separate the patient's inherent capacity to perform actions within a domain and performance in his or her actual environmental context.[7] *Capacity* refers to the environmentally adjusted inherent ability of the individual or, in other words, the highest probable functioning of a person in a given domain at a given point in time, in a standardized environment. Capacity can be measured by physical tests or by questionnaires that ask, "Can you?" Performance describes what a person actually does in her or his current environment and thus describes the person's functioning as observed or reported in the person's real-life environment with the existing facilitators and barriers.[8] Performance can be measured by direct observation. However, as visual observation is often highly impractical, self-report measures can be substituted that ask, "Do you?" Increasingly accelerometers are being used to get some objective sense of a person's activity and sedentary level.

The rehabilitation problem solving (RPS) form is based on the ICF[9] and is a practical tool to use to visualize the patient's state of functioning and disability. The form is used to specify precise and relevant target problems, discern factors that cause or contribute to these problems, and plan the most appropriate intervention. In addition, the form was designed as a tool to facilitate both intra- and interprofessional communications and improve the communication between healthcare professionals and their patients.[9] The form is divided into three parts: (1) the header provides basic information, (2) the upper part is used to describe the patient's perspective, and (3) the lower part is used for the analysis of the healthcare professionals.

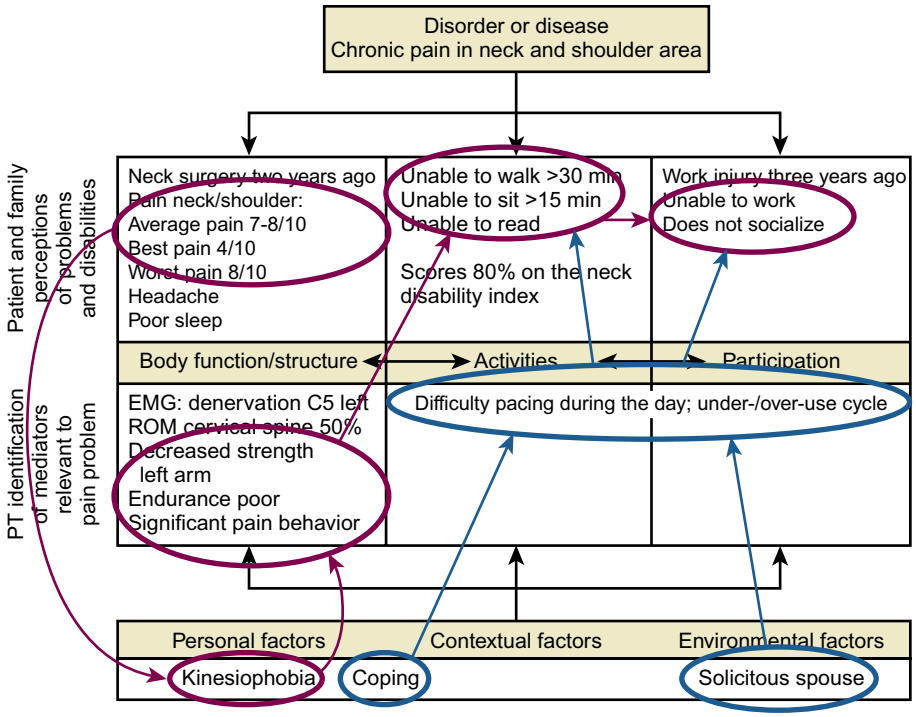
The form can visualize the current understanding of the patient's state of activities and participation, his or her target problems, and how the healthcare team relates them to hypothetical mediators and contextual factors (Fig. 60.2).

From the information obtained through carefully selected questionnaires, an interview, the physical examination, and physical tests, most of the information needed to develop an appropriate treatment plan should be obtained.

Patient Interview

The Joint Commission on Accreditation of Healthcare Organizations requires that all patients have the right to an adequate pain assessment, including documentation of pain location, intensity, quality, onset/duration/variations/rhythms, manner of expressing pain, pain relief, what makes it worse, effects of pain, and a pain plan. Besides questions about the location, intensity, frequency, and duration of pain, questions such as "What do you think causes your pain?" and "What is the worst thing you think might happen to you because of your pain?" will give insight into the patient's belief system—especially important if the patient comes from a different culture—and the presence of catastrophizing. In addition, rehabilitation specialists focus on determining how much the pain interferes with activities and participation: activities of daily living such as housework, grocery shopping, and getting around in the community; recreational and social activities; and the ability to do work and sleep. For example, the number of hours lying down and changes in activity level because of pain during a day is noted. Patients are further asked about significant others, partners, parents, and children; do they help out, ignore the patient, or prevent them from doing things as they fear the patient might "harm" him- or herself.

Unfortunately, there are no perfect measures of physical activity or activity limitations. Comparison measures include both "subjective" measures (based on self-report) and "objective" measures (based on direct measurement). Self-report measures can be self-administered or interviewer administered, both in person and on the telephone. However, self-report of physical activity can reflect a difference between how active patients really are and how active they perceive they are, resulting in a



• **Figure 60.2** Rehabilitation Problem Solving (RPS) form used for a patient with chronic neck and shoulder pain. *EMG*, Electromyelogram; *PT*, physical therapist; *ROM*, range of motion. (Adapted from Steiner WA, Ryser L, Huber E, et al. Use of the ICF model as a clinical problem-solving tool in physical therapy and rehabilitation medicine. *Phys Ther.* 2002;82:1098–107.)

difference between self-reported physical activity level and the actually observed active behavior.[10] Studies, including self-report and objective measures on activity and activity-related disability, indicated a gap between self-report and objective measurement.[11] In rehabilitation practice, there is a tendency to use objective and self-report measures to assess physical activity. Objective measures include functional capacity tasks, markers of movement (accelerometers, registration of activity by smartphone, or activity monitors), and observed or videotaped activity (direct observation).[12] Self-reported status often involves outcomes of most relevance and importance to patients and their loved ones because they capture patient experience and perspective.[13] Rehabilitation professionals should know these differences during their assessment. Besides assessing a patient's level of activity, labeling a patient's activity-related behavior style seems of additional value when choosing the most appropriate ingredients for treatment: Will this patient avoid activities because of pain (avoider), or will he or she persist in the performance of activities regardless of pain (persister)?[14]

Psychosocial factors have been found to have a significant impact on perceived disability, particularly among persons with chronic pain. The rehabilitation professional's observations of a patient's behavior during the interview or functional testing as a part of a screening procedure can deliver valuable information and should be communicated clearly to the rest of the team, which can then direct appropriate psychological and psychiatric treatment. Psychological screening by rehabilitation professionals with history taking has been shown to have low sensitivity and predictive value for identifying distressed patients. Thus formal screening of some sort, such as with a questionnaire, is recommended.[15] Psychosocial factors contributing to a patient's disability level that can be assessed by a questionnaire are, for instance, fear of movement[16] (Tampa Scale of Kinesiophobia),[17] catastrophizing (pain catastrophizing scale[18]), and depression (the Beck depression inventory).[19] High pain catastrophizing has also been found to be a predictor for patient dropout during treatment.[20] As previously mentioned, particularly important are questions about what the patient expects from treatment. Patients' beliefs and expectations play a large role in treatment participation and eventual treatment outcome. Studies have shown that high patient expectations may positively influence clinical outcomes independent of the treatment itself.[21] Treatment of chronic pain is often complex and may be further complicated when patients and healthcare providers have differing goals and attitudes concerning treatment. Difficulties in engaging in collaborative treatment decision making may result. A negative expectation on treatment outcome can influence treatment compliance. For instance, a patient who is looking for pain relief only and insists on medication management as the sole treatment for the pain is not likely going to comply with a rehabilitation program. Efforts to enhance patient-provider communication as well as to systematically examine non-specific treatment factors are likely to promote effective management of chronic pain. This includes adapting health information to the level of patients' health literacy by not using medical jargon, not delivering too much information at a time, and confirming patients' understanding of what was discussed by using teach back techniques.[22] Unfortunately, despite the widespread recommendations to medical practitioners to check patients' understanding directly, it does not yet appear to be routine practice.[23]

Physical Examination

The traditional rehabilitation-oriented physical examination assesses impairments in joint range of motion (ROM), strength, neurologic integrity, and gait. Diagnostic procedures should

focus on identifying potentially serious "red flag" conditions that require prompt medical evaluation. The main objective is to determine whether there is a relationship between pain reports and objective physical findings or whether the patient presents with chronic primary pain or chronic secondary pain.[24] In the former, rehabilitation might focus on improving physical functioning in general and have a more significant behavioral approach. In contrast, in the latter case, rehabilitation might focus more specifically on impairments related to pain that interfere with the ability to function.

Patient anxiety may complicate the physical examination. Catastrophic cognitions, behavioral displays of pain, and somatic sensations measured during examination have been shown to uniquely predict anxiety experienced during examination.[25] Muscle guarding and pain behaviors are often displayed during physical examination and include moaning, sighing, rubbing, reluctance to perform any active movement (ROM), and the presence of giveaway weakness and non-physiologic signs. Waddell's non-physiologic or behavioral signs in patients with back pain can be assessed through palpation and simulation tests,[26] including axial loading (pressure applied to the top of the patient's head), simulated rotation (moving shoulders and hips together so that no rotation occurs in the trunk), inconsistency between the straight leg raise in a sitting versus supine position, giveaway weakness with resisted muscle testing, and regional sensory change. Several studies examined the cross-sectional construct validity of the Waddell score and found evidence that it measures a combination of pain intensity, illness behavior, physical dysfunction, and psychological functioning,[27] somatic over-reporting,[28] increased perceived disability, and pervasive pain interference.[29] Recognizing that studies in patients with chronic pain have identified discrepancies between self-report of physical activity and actual level of physical activity, capacity testing is performed in addition to traditional impairment examination. This involves direct observation of patient performance on specific tasks and assessment of whether the patient is willing to move or fears performing specific tasks. Baseline functional ability assessment can provide objectively verifiable information about a patient's quality of life and ability to participate in normal life activities.

Functional tests can be used to focus on performance in basic daily life activities, such as walking, stair climbing, and lifting. Various specific tasks or sets of tests that intend to represent daily functioning are available for this purpose. Simple tasks such as 5 min walking, 50 foot walking, sit-to-stand, 1 min stair climbing, loaded forward reach, or various lifting tasks are available to test a patient's capacity during one specific activity. However, the ability of the tests to reflect the level of functioning in patients with pain has to be taken with caution. The test-retest reliability[30] and responsiveness appeared to be only moderate for most of the tests.[31] In addition to single tests, test batteries have been introduced to represent functioning in patients with pain. For example, the Back performance scale is a condition-specific performance measure of activity limitation in patients with back pain and includes five tests of daily activities requiring mobility of the trunk: sock test, pickup test, rollup test, fingertip-to-floor test, and lift test. The psychometric properties of this test battery have been demonstrated.[32,33] A second example is a generic test battery that includes nine physical performance tests: the time taken to complete various tasks (e.g. picking up coins, tying a belt, reaching up, putting on a sock, standing from sitting, a 50 foot fast walk, a 50 foot walk at preferred speed), the distance walked in 6 min, and the distance reached forward while standing. The reliability and discriminant ability of this battery has been confirmed.[34]

In the assessment of work related performance, a functional capacity evaluation (FCE) is often used.[35,36] An FCE is an evaluation of the capacity of activities that are used to make recommendations for participation in work while considering the person's body functions and structures, environmental factors, personal factors, and health status.[37] The purpose of an FCE is to test a person's physical abilities to the maximum to produce objective documentation regarding work and activities of daily life. The FCE has become part of the accepted practice in work injury prevention and rehabilitation.[38,39] During an FCE, the patient has to complete a standard protocol of physical tasks while a trained observer records the capacity and limitations. Assessment includes the ability to lift weights from the floor to waist and from waist to overhead, carry, crawl, squat, sit, stand, walk, climb stairs, and push and pull weights. Aerobic capacity may be determined from a maximal bicycle or treadmill test. Additional specific tests may be performed, such as those used to evaluate fine motor skills for the hands and handgrip strength. Practical data on the use of FCEs to determine an individual's physical capacities have been available since the early 2000s, and normative data have now been established.[36] Biopsychosocial factors may influence functional test and FCE test results, although it is unclear to what extent and which factors are important. A systematic review concluded that there is conflicting evidence for the influence of psychological factors and absence of evidence for the influence of social and biologic/physiologic factors in patients with non-specific chronic low back pain (CLBP) that influence capacity test results.[40] Therefore interpretation of FCE test results is not entirely objective because the observer has to decide if a patient performed maximally or submaximally during the test. In addition, pain and pain related constructs have been shown to negatively influence FCE performance levels. FCE should thus not be considered a purely "objective" indicator of functional impairment independent of subject or evaluator perceptions.[41]

Several studies have shown that self-report and performance and capacity tests, although related, appear to tap into different aspects of the physical functioning domain.[11] For instance, patients with CLBP showed considerable differences in limitations when comparing self-report, clinical examination, and functional testing for assessing work related limitations. Professional healthcare workers should be aware of these differences when using them in daily practice.[42,43]

Therapy for Chronic Pain

An important difference between patients with acute pain and those with chronic pain is the variation in relationships between pain, activity limitations, and participation restrictions. For patients with acute pain, nociception, perceived pain, activity limitations, and participation restrictions often have a close relationship. Therefore treatment in the acute phase focuses on eliminating the causal factor of the pain, resulting in a reduction of activity limitations and the prevention of disability. However, for patients with chronic pain, this treatment strategy is often insufficient. Patients with chronic pain may never return to work even when the only impairment identified is pain. Treatments that address chronic pain as a warning of tissue damage, like in acute pain, do not alter the illness and disability behavior of patients with chronic pain, nor will they improve their health-related quality of life. The focus of therapy should be to help these patients regain control

over their lives by active participation in their pain management program and learning to cope with pain. To achieve this goal, an active partnership is needed between the patient and the rehabilitation professional. Like other patients, patients with chronic pain want a confidence-based association that includes understanding, listening, respect, and being included in decision making.[44] The input from the interview and patient assessment form the basis of shared decision making, which involves at least two participants who engage in a process of both mutual information and interactive discussion. Patient participation should result in a greater sense of personal control, more satisfaction with treatment, better compliance, and transfer into the daily routine of disease management and, consequently, better outcomes.[45]

Patients with chronic pain are not a homogeneous group, and there is no magic bullet that fits all. Because each patient has a unique set of circumstances, psychosocial issues, and physical findings, treatment is individualized and based on the comprehensive assessment of the patient and the patient's individual goals.

Chronic pain management should include:[46]

- collaboration between the rehabilitation professional and the patient
- a personalized rehabilitation plan
- tailored education of the patient on the nature of the problem
- resolution of treatable barriers related to functional goal attainment
- tailored instruction in independent management of pain
- instruction in methods to prevent future problems
- monitoring of outcome (achievement of patient goals)
- monitoring of adherence to treatment
- planned follow up

Collaboration Between the Rehabilitation Professional and Patient

Implementing patient centered approaches in caring for individuals with chronic pain and using principles drawn from the chronic disease management model to improve care systems may improve patient and provider satisfaction with chronic pain care.[47] For instance, significant positive associations were found between a positive therapeutic alliance and the patient's global perceived effect of treatment, change in pain, physical function, patient satisfaction with treatment, depression, and general health status in patients with chronic musculoskeletal pain in physical rehabilitation.[48] Contributing to a positive therapeutic alliance are (1) therapist-patient agreement on goals of treatment, (2) therapist-patient agreement on intervention, and (3) the affective bond between patient and therapist.[48] Several studies indicate that a patient's perception of a provider's engagement and concern impacts their perceived satisfaction more than improved health.[49]

Coming to a mutual agreement on goals and intervention can be a challenge. To decrease the negative impact of chronic pain on functioning and health-related quality of life, patients must adopt self-management skills. In order to do so, in case of persistent non-reducible pain, patients have to be ready to stop focusing on further medical diagnostics to find a definite medical solution for pain and change to an active orientation regarding self-management. Not all patients are ready for this. For a good collaboration between the physical therapist and the patient, the patient must at least be planning to take an active orientation toward self-management, and the therapist should support and encourage this goal. Exercise improves pain and function in people with persistent musculoskeletal pain (PMSK), but adherence is often poor. Evidence suggests that exercise behaviors are modifiable, and behavior initiation and maintenance may be enhanced with behavior change interventions.[50,51] In a systematic review on behavior change techniques (BCTs) associated with adherence to prescribed exercise in patients with persistent musculoskeletal pain, a moderate level of evidence to support adherence for five BCTs was found, including (1) Social support (unspecified), (2) Goal setting (behavior), (3) Instruction of behavior, (4) Demonstration of behavior, and (5) Behavior practice/rehearsal. Treatment groups including seven or fewer BCTs, which were unique to any BCTs used in the control group, were most effective at enhancing exercise.[52]

Not only do patients bring expectations about treatment, but the provider does as well. Treatment decisions are often heavily influenced by the personal beliefs of the provider. Several studies have indicated that the personal attitudes and beliefs regarding pain of rehabilitation professionals and other healthcare providers are associated with their advice to patients regarding regaining activities and return to work. Practitioners with a more biomedical orientation are more likely to use a pain-contingent treatment approach and focus on "curing" impairments, whereas practitioners with a more biopsychosocial orientation will more likely use a time-contingent treatment approach and focus on increasing activities. Linton and associates investigated the level of fear avoidance beliefs in practicing general practitioners and physical therapists.[53] Compared to providers with low fear avoidance, providers with high levels of fear avoidance belief had an increased risk for believing sick leave to be a good treatment, not providing good information about activities, and being uncertain about identifying patients at risk for developing persistent pain problems. The combination of a high fear avoidant provider with a high fear avoidant patient seems a recipe for disaster in chronic pain management and should at all costs be avoided.

Different assessment tools are currently available to measure practitioners' beliefs toward pain, such as the Attitudes to Back Pain scale for musculoskeletal practitioners (ABS.mp), the Healthcare Providers' Pain and Impairment Relationship Scale (HC-PAIRS), and the Pain Attitudes and Beliefs Scale for Physiotherapists (PABS.PT).[54]

It can be concluded that for optimal interaction with his or her patient, a rehabilitation professional should have (1) a dynamic, multidimensional knowledge base that is patient centered, (2) a clinical reasoning process that is embedded in a collaborative, problem solving venture with the patient, (3) a central focus on movement assessment linked to patient function, and (4) consistent virtues seen in caring and commitment to patients.[55]

Personalized Rehabilitation Plan

To win the collaboration of patients and their families, rehabilitation professionals need to negotiate and agree on a definition of the problem they are working on with each patient. They must then agree on the targets and goals for management and develop an individualized, collaborative self-management plan.[46] The patient and rehabilitation professional need to agree on the goals of treatment to prevent confusion and disappointment on both sides and to establish a collaborative relationship. Adopting a shared decision making approach to goal and treatment setting may be useful. Training and support for both health professionals and patients may facilitate a shared decision making approach.[56] Establishing specific but attainable goals can facilitate task

performance. Unrealistic goals can lead to decreased motivation and a sense of failure. Self-efficacy facilitates goal setting. People with high self-efficacy choose to perform more challenging tasks.[57] They set themselves higher goals and stick to them. Self-efficacy can be understood as the confidence one has in one's ability to deal with certain life stressors. High self-efficacy is related to better treatment outcomes, such as higher levels of physical functioning and the use of pain coping strategies related to better adjustment to chronic pain.

Linking goals to patient values (value-based goals) should help in achieving those goals, as values (the things that are important to us) are one of the predominant determinants of how we choose our goals. Goals can be thought of as stepping stones that move patients toward their values. Goals must be measurable so that treatment can be time limited and have an observable end point. Return to a pain-free state is a good example of an unrealistic goal. Common (realistic) goals are associated with a reduction of the impact of pain on the patient's life (i.e. increased level of activities and participation), independent pain management, and the attainment of functional goals. Examples of functional goals are being able to walk for an hour, sitting through a meal or a movie, being able to carry and lift a certain amount of weight, playing with the kids, going out with the family, and being able to perform essential job components. Return to work or vocational rehabilitation should be part of the treatment plan when appropriate. Goals must be realistic and attainable within a reasonable time. A gauge such as the Canadian Occupational Performance Measure can be helpful during the process of goal setting and goal attainment during treatment.[58] It is helpful to determine the number of treatments per week and the number of weeks of treatment before initiating treatment (i.e. treatment will occur three times per week for six weeks). Having a definite end point increases patient adherence and provides a framework to the patient and the treatment team in which to achieve goals. A treatment contract that includes goals, the intensity and frequency of treatment, and expected compliance with treatment can be helpful.

During treatment, the use of goal setting charts is recommended. Patients set a target for activities each week, record their achievements on the chart, note the nature of any difficulties and how these will be tackled next time, and make other comments. Patients may comment on their performance or on the appropriateness of the goals they had set. In this manner, they can monitor their progress and improve their accuracy in goal setting.

Education on the Nature of the Problem

Several studies have shown that most patients expect an explanation or an improved understanding of their pain problem, a clear diagnosis of the cause of their pain, information, and instructions. They expect confirmation from the healthcare provider that their pain is real.[2,44] For patients attending pain clinics, the explanation of their pain problem is rated as important as the cure or relief of their pain.[2] Evidence from systematic reviews shows that reconceptualizing pain improves patients' knowledge of pain biology, reduces catastrophizing thoughts, and improves pain and function.[59–63] Education on the neurophysiology of pain seems important and may be considered a precondition for pain management success.[61,63,64] The sensitization model can be used to explain pain as a physical cause related to changes in the nervous system and to explain how chronic pain exists without tissue damage. This explanation may improve the patient's motivation to discuss the importance of psychosocial factors that contribute to the maintenance of chronic pain. However, not all patients benefit. For some patients, the message about danger signals and the brain is too abstract. These patients may benefit from "learning by doing" or from cognitive behavior therapy and educational programs that are simplified for reading ability, which have been shown to result in improved pain and physical functioning in children with chronic pain and adults with chronic pain and limited health literacy.[65,66]

The main goals of education are reassurance and empowerment for further treatment. Do not utilize patient education and counseling strategies that either directly or indirectly increase the perceived threat or fear associated with low back pain, such as in-depth, pathoanatomic explanations for the specific cause of the patient's (low back) pain.[67] When treating patients in a group, education comes from other patients as well. They may share solutions to functional problems, ways to better pace their activities, or independent pain management techniques they have found helpful.

Resolution of Treatable Barriers Related to Functional Goal Attainment

Barriers related to the attainment of functional goals in patients with chronic pain are usually because of a combination of physical factors and patient beliefs and cognitions. Physical conditioning programs that include a cognitive behavior approach plus intensive physical training (specific to the job or not) that includes aerobic capacity, muscle strength, endurance, and coordination; are in some way work related, and are given and supervised by a rehabilitation professional, or a multi-disciplinary team seem to reduce the number of sick days for some workers with chronic back pain when compared to usual care.[68,69] Ideally, exercise therapy is combined with a cognitive behavior approach in a chronic pain rehabilitation program.

Exercise Therapy

The "deconditioning syndrome"[70,71] was postulated in the mid-1980s as a factor contributing to the intolerance to physical activities and subsequent (further) loss of function and disability in patients with chronic pain. Physical disuse has been presented as one factor that perpetuates chronic pain in theoretical pain research models. Although current evidence does not support the disabling influence of a deconditioning syndrome in chronic pain syndromes,[72] reconditioning is still used as a foundation for various pain rehabilitation programs. Enhancing physical activity and fitness can indeed have a beneficial effect on patients with chronic pain. For example, meta-analyses have demonstrated strong evidence for the efficacy of muscle conditioning and aerobic exercise to lessen symptoms in persons with arthritis, other rheumatic diseases,[73] and shoulder pain.[74] There is evidence (although the studies have been classified as low quality) for the effectiveness of exercise therapy compared to usual care in patients with back pain.[75]

Exercise therapy encompasses a heterogeneous group of interventions, and several studies have found beneficial effects of exercise on pain and function. However, there continues to be uncertainty about the most effective exercise approach. Most studies had insufficient data to provide useful guidelines on optimal exercise type or dosage, although some evidence exists that "sicker" patients may benefit from more intensive treatment. Haldorsen and associates,[76] for instance, showed that

patients with a poor return to work prognosis returned to work at significantly higher rates when they completed a more intense multi-disciplinary treatment program. In contrast, patients with a good return to work prognosis benefited equally from ordinary treatment and multi-disciplinary treatment. Patients thus do not all benefit from the same exercise program. Therefore exercise programs need to be designed and tailored to the individual needs of the patient. In addition, the mechanisms by which physical treatment supports improvement in patients with chronic pain may not only be based on changes in muscle strength or fitness. In a study of Smeets and coworkers, it appeared that pain catastrophizing mediated results in both cognitive behavior treatment and physical treatment.[77] Changes in the level of catastrophizing, instead of changes in physical fitness, were associated with changes in disability during treatment.

Little evidence supports the use of passive modalities in the treatment of patients with chronic pain. High-quality evidence suggests that there is no clinically relevant difference between spinal manipulative therapy and other interventions for reducing pain and improving function in patients with CLBP.[78] There is currently insufficient evidence to draw a firm conclusion on the clinical effect of low-level laser therapy, massage, traction, superficial heat/cold, and lumbar supports for patients with CLBP.[75] Systematic reviews and meta-analyses on transcutaneous electrical nerve stimulation (TENS) are contradictory, reporting TENS does not improve symptoms of lower back pain, but may offer short term improvement of functional disability,[79] offer significant pain reduction in CLBP,[80] and inconclusive evidence of TENS benefits in patients with LBP because of the low quality of the studies.[81]

Passive modalities (TENS, ultrasound, massage, corsets, traction, acupuncture) should be limited and used only combined with an active exercise program.

Cognitive Behavior Approach

Cognitive behavior therapy (CBT) is a combination of cognitive and behavioral therapy. Behavioral therapy addresses the connections between situations and patients' habitual reactions to them (i.e. walking with a limp because it gets positive attention from the spouse). Cognitive therapy addresses patients' thoughts or beliefs that cause them to feel and act the way they do ("If I use my back, I will become paraplegic, so the safest thing to do for me is to lie on the couch and do nothing"). Therefore if patients exhibit unwanted behaviors, it is important to identify the beliefs that cause the behaviors and to teach patients how to replace or modify the beliefs so that more desirable behavior might ensue.

Cognitive-behavior modification can be accomplished in several ways: by talking about beliefs, by gaining exposure to avoided activities, by increasing the number and duration of usual activities, by participating in a "reward system" in which healthy behavior is rewarded and encouraged, and non-healthy behavior is ignored, and by listening to feedback from other patients on their behavior.

Pain related fear has been consistently associated with the initiation and maintenance of chronic pain disability.[82] For patients with high levels of pain and activity-related fear who avoid activities, behavioral methods such as graded activity and graded exposure treatment have both been shown to be effective in reducing disability.[83] Repeated exposure to avoided activities decreases anxiety and fear about them. In graded exposure, patients are challenged to perform the specific physical activities that they believe will harm them. Most of the time, exposure treatment is performed in combined therapy with a physical therapist and a behavioral therapist.

Although multi-disciplinary programs have shown effectiveness in patients with chronic pain,[84] it is still unclear which component is most effective. In a study in which the effectiveness of three rehabilitation interventions (an active physical, cognitive behavior, and combined treatment) for patients with CLBP was compared with that for a waiting list control group, it appeared that all three active treatments were effective in comparison to no treatment. However, no clinically relevant differences between the combined and the single-component treatments were found.[85] A new approach in CBT, or the third-wave CBT, has been introduced in pain treatment. An example of a third-wave CBT approach is acceptance commitment therapy (ACT). ACT differs from traditional CBT in that instead of trying to teach people to better control their thoughts, feelings, and sensations. ACT teaches them to "just notice," accept, and embrace personal life events. ACT aims to help individuals clarify their personal values and take action on them to bring more meaning to their lives.[86] ACT may be a helpful alternative to traditional CBT because of its shift of emphasis from trying to reduce or control the experience of pain to a focus on valued action in the presence of pain. Acceptance of chronic pain requires that an individual maintain functioning and participate in enjoyable and reinforcing activities in daily life even while continuing to experience sensations of pain. Random effects meta-analyses found small to large effects on the range of outcomes favoring ACT over control conditions at posttreatment.[87]

Self-Management Techniques

Self-management is as yet a difficult to measure complex concept.[88] To maintain sufficient quality of life, successful self-management—the ability to manage symptoms, treatment, physical, psychological and social consequences, and lifestyle changes related to one's chronic condition—is essential. Self-management skills include problem solving, decision making, resource utilization, forming a partnership with a healthcare provider and taking action.[89] To date, generic self-management interventions have been shown to have limited effectiveness for patients with chronic musculoskeletal pain.[90] However, there is emerging evidence that for participants with non-headache conditions, psychological therapies delivered via the Internet reduce pain, disability, depression, and anxiety post-treatment. The positive effects on disability were maintained at follow up. These effects are promising, but considerable uncertainty remains around the estimates of effect.[91]

Instruction in Methods to Prevent Future Problems

It is almost inevitable that a patient with chronic pain will experience an exacerbation of the pain problem. Relapse may be because of an individual physical event, or it may result from cumulative physical and psychological stresses that challenge patients' coping resources. The rehabilitation professional can help to identify situations that are challenging and develop strategies to cope with them. Strategies may include setting criteria to visit health professionals, using pain medication, or briefly resting and relaxing. Plans for resuming activity following an exacerbation are critical.[92]

Technologic applications, such as apps, virtual reality, or telephone-based interventions, may help patients maintain the skills they learned in their pain management programs and prevent relapse.

If returning a patient to work is an important goal, a job description with as much detail as possible provides important ergonomic information. Patients can then practice components of the job description with the physical therapist and at home.

The goal of ergonomics is to ensure that the workplace is designed to prevent work-induced injuries. Non-neutral postures, forceful exertions, constrained or static postures, repetitive work, use of pinch grip, work over shoulder height, prolonged periods with the trunk inclined forward, heavy lifting, twisting while lifting, and whole body and vibration are all risk factors for work related musculoskeletal disorders. A common type of ergonomic instruction is educating the patient on manual handling and lifting, optimal seated postures and activities, and the relationship of the seat to the workbench or desk. The patient is taught to take "stretch breaks" during work or to alternate job components.

At the end of treatment, a vocational assessment is advised, which preferably includes an FCE assessment. Then the FCE is matched with the job description. Recommendations for return to work are based on this evaluation. Changes in the job that would enable the patient to return to work may be suggested. If possible, a worksite analysis also should be performed to help identify risks to the patient and to suggest changes to the work environment to accommodate the patient.

A "light duty" job or a gradual increase in the hours worked per day is usually recommended for a return to work. Some therapists offer a "work hardening" program in which a pain patient gradually "works" up to a simulated 8 h workday. In workers with chronic back pain, pooled results of five physical conditioning studies showed a small effect on sickness absence at long-term follow up. The addition of cognitive behavior therapy to physical conditioning programs was not more effective than physical conditioning alone. Workplace involvement might improve the outcome.[69] After discharge from these programs, a full-time return to work is appropriate.

Monitoring of Outcome (Achievement of Patient Goals)

Generic and disease-specific measurement tools have been developed. Recommendations based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) can be helpful for designing sets for routine assessments to monitor treatment progress.[93] Important domains to consider for assessment as advised by IMMPACT are pain, fatigue, disturbed sleep, physical functioning, emotional functioning, patient global ratings of satisfaction, and health-related quality of life. In addition, patients' treatment goals can serve as outcome measures to determine treatment efficacy. A simple visual analog scale can visualize progress, for instance:

In the past week, were you able to walk a mile?

Completely unable_____Completely able

Monitoring of Adherence to Treatment

As early as 1990, Turk and colleagues reported that nonadherence with therapeutic recommendations during treatment and subsequent to treatment termination are neglected topics in the treatment of patients with chronic pain.[92] The topic remains under-researched.

Besides outcome domains mentioned earlier, IMMPACT focuses on participant disposition (e.g. adherence to the treatment regimen and reasons for premature withdrawal from the trial). Adherence to pain management treatment recommendations and the number of "no shows" should be monitored in clinical practice. Rehabilitation professionals need to offer an appropriate behavioral framework by maintaining a clear structure, consistent rules, and rewards for a positive patient response during treatment. When a patient is persistently nonadherent, the problem should be addressed, and the reasons for nonadherence explored. Reasons for nonadherence can include poor satisfaction with treatment results or a patient-provider relationship that does not work well.

Planned Follow Up

There is a paucity of literature on planned follow-up after multidisciplinary treatment. Planned follow up can be done individually or in group settings and serves to prevent crisis management. It can also serve as an external motivator (they are going to know I did not do my exercise/self-management techniques). However, there is no evidence as to the optimal frequency or duration of follow up visits to date.

Conclusion

Generally, the evaluation and treatment of chronic pain patients are difficult tasks that are best performed in an interdisciplinary team setting because both biomedical and psychosocial aspects related to the pain problem have to be addressed. Therefore the role of the rehabilitation professional is to form a close partnership with patients, help patients set and attain individual goals at activities and participation levels, and teach patients self-management skills. Ultimately, patients should become experts in managing their own chronic pain in order for them to enjoy the best health-related quality of life possible.

Key Points

- Interdisciplinary care of patients with chronic pain has proven to be of significant value.
- A collaborative relationship between patients and rehabilitation professionals is essential to enhance successful outcomes.
- The pain management treatment plan must be tailored to the individual patient.
- Establishing treatment goals, patient education, therapeutic exercise, and behavioral techniques are at the core of rehabilitation management.
- Active involvement of patients and treatment adherence are necessary.

Suggested Readings

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The Integrative Approach to Pain Management

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Integrative Medicine: Overview

Integrative Medicine is a philosophy of care that integrates conventional allopathic medical therapies with modalities not typically included in conventional care and addresses the physical, emotional, and spiritual needs of the patient. This field of medicine is sometimes referred to as complementary medicine or complementary and alternative medicine. However, these terms refer more precisely to modalities, such as acupuncture, meditation, nutritional supplements, and massage, all of which may be included in the integrative medicine "toolbox." Some organizations are now using the term "integrative medicine and health" to highlight the field's emphasis on personal and community health promotion. The Academic Consortium for Integrative Medicine and Health defines integrative medicine and health as follows: "Integrative medicine and health reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing."[1]

In the past several decades, there has been an increased interest in use of and body of research evaluating the integrative approach to care, and many medical schools now include integrative medicine topics in their curricula. An increasing body of evidence suggests that integrative medicine can be helpful in the management, and even prevention, of many chronic illnesses that negatively impact individual wellness, societal wellness, and financial burden on the United States healthcare system. In 2011 the Bravewell Collaborative initiated a survey to clarify how integrative medicine was being practiced in the United States.[2] Twenty-nine integrative medicine programs participated.

The most commonly employed practitioners were physicians, massage therapists, meditation instructors, and acupuncturists. The most common interventions prescribed were, in descending order, as follows:

- Nutritional interventions
- Dietary supplements
- Yoga
- Meditation
- Traditional Chinese Medicine/acupuncture
- Massage
- Pharmaceuticals

The survey identified five conditions that the respondents felt were the most effectively treated at their integrative medicine centers: chronic pain, gastrointestinal conditions, depression, stress, and cancer. There was significant consistency across centers in the use of specific interventions for particular clinical conditions, which suggests that a common knowledge base has emerged to guide integrative clinical care. In addition, 72% of the programs provided self-care/wellness experiences for their practitioners and staff. Integrative medicine incorporates conventional and complementary treatments and attends to the mind, body, spirit, and community of the patient, family, and practitioner.

Physicians may recommend complementary approaches to their patients, or patients may seek them out on their own. In one recent study,[3] massage therapy was the modality most frequently suggested by clinicians to their patients, followed by chiropractic/osteopathic manipulation, herbs/non-vitamin supplements, yoga, and acupuncture. Over 50% of physicians recommended at least one complementary approach to their patients in the previous year. Comparison of complementary modality usage over time (2002–2012) revealed that dietary supplements (particularly fish oil and glucosamine/chondroitin) remained the most popular modality across periods, with deep breathing exercises being the second most commonly used approach.[4] The use of yoga, tai chi, and Qigong increased linearly over the measured time period, and chiropractic/osteopathic manipulation and meditation were also commonly used. Ayurveda, biofeedback, guided imagery/hypnosis, and energy healing were low and had no significant change over time.

Pain syndromes, such as chronic back pain, are associated with significant healthcare costs.[5] Unresolved pain has a wide-reaching impact, affecting physical, emotional, and spiritual wellness and negatively impacting social and occupational functioning. Integrative medicine, which adopts a mind-body approach to the treatment of pain and employs multiple effective complementary modalities, is well-suited to address chronic pain syndromes and may result in decreased healthcare costs.[6] Chronic pain is one of the most common reasons that people use complementary and integrative medicine modalities,[7] and acupuncture, mind-body modalities, dietary interventions, and herbs/supplements are common choices. Complementary and integrative pain management strategies are also used for cancer pain[8] and in community-dwelling older adults.[9]

Multidimensional Perception of Pain

The perception of pain is multifactorial and involves a complex interplay between the peripheral and central nervous systems. As pain signals reach the brain from the periphery, the brain can

modify these signals by activating the inhibitory pathways and releasing substances such as endorphins and neurotransmitters. Alternately, the brain can magnify nociceptive signals if they are perceived to be threatening, thus increasing the perception of pain. Pain has both nociceptive and affective components; thus emotion and pain are deeply intertwined.[10] The connections between the cerebral cortex and the limbic system allow the brain to give meaning to the pain experience. It is this connection between emotions and pain perception that forms the basis of the mind-body approach to pain. Psychological factors such as the tendency to catastrophize have been associated with chronic pain,[11] and pain catastrophizing is associated with reduced health-related quality of life.[12] Overall, multiple psychosocial variables impact the likelihood of developing chronic pain, the ability to cope successfully despite pain, and the effectiveness of pain treatments.[13] These variables include childhood trauma, negative affect, level of social support, pain catastrophizing, self-efficacy, and more.

Life stress in childhood[14] or adulthood[15] can be associated with adult pain syndromes, and anxiety and chronic pain often coexist.[16] Depression and pain are related, with each negatively impacting the other. The serotonergic and norepinephrine systems are important in modulating both depression and pain, which is illustrated by the pain modulating properties of serotonergic and norepinephrine anti-depressants.[17] Untreated pain may lead to depression, and untreated depression can exacerbate pain. Even brief interventions designed to address emotional components of pain have been effective in decreasing pain severity.[18]

The prefrontal cortex (PFC) is important in pain processing. It interacts with other parts of the brain, such as the amygdala, hippocampus, thalamus, and others. Acute and chronic pain can result in changes to the PFC, including alterations in neurotransmitter release, gene expression, and inflammation, which can impact the PFC's structure, activity, and function.[19] The biopsychosocial model of pain management takes advantage of this interaction between the PFC and other emotion-regulating regions of the brain. Interventions such as cognitive behavioral therapy, mindfulness, music, meditation, exercise, and others may help to regulate the emotional centers of the brain and thus help to manage pain.

Similar regions of the brain are activated by both emotions and pain.[20] Neuroimaging studies have shown that social pain and physical pain are reflected similarly in the brain. In one study, subjects played a virtual game that elicited feelings of being excluded. The anterior cingulate cortex showed an increase in activity during exclusion, including physiologic changes that are similar to those seen with physical pain.[21] In addition, hypnotic suggestion of pain has been shown to create changes on functional MRI in the anterior cingulate cortex, thalamus, insula, prefrontal cortex, and parietal cortex, which are also influenced by pain originating in peripheral tissues.[22] This suggests that pain initiated by the brain has significant similarity to pain originating in the periphery. This concept highlights the mind-body connection and is important for the understanding and treatment of patients with acute and chronic pain.

People with chronic low back pain have an impaired ability to inhibit their pain. This may be related to decreased activation of the anterior cingulate cortex and prefrontal cortex, components of the descending inhibitory system, as well as decreased activation of the nucleus accumbens, which is involved in the dopamine system and thus the release of endogenous opioids.[23] Techniques that enhance active coping and recruitment of certain brain regions may be helpful with pain regulation. Neurofeedback is an example of such a technique. In one study, 28 subjects used fMRI neurofeedback while receiving a heat-induced pain stimulus. Successful pain coping was positively correlated with activation in the anterior cingulate cortex, prefrontal cortex, hippocampus, and visual cortex.[24] Mindfulness meditation (MM) was found to be more helpful for people with higher baseline pain catastrophizing, while mindfulness based cognitive therapy (MBCT) was more helpful for people with lower baseline pain catastrophizing. MM is a breathing practice that encourages focused awareness and attention on the current moment without getting carried away by thoughts, while cognitive behavior therapy (CBT) focuses on how your thoughts, feelings, and behaviors influence one another. MBCT combines dimensions of MM and CBT. Thus certain tools may be more effective for some patients than others, and a multimodal targeted approach is ideal.[25]

Integrative Medicine Modalities and Pain

Varied complementary medicine techniques have shown benefits in the treatment of pain. Domains such as Traditional Chinese Medicine, mind-body medicine, manual medicine, and others have an increasing body of evidence supporting their use in pain management. The most commonly used and well supported modalities are discussed below.

Acupuncture and Traditional Chinese Medicine (TCM)

TCM is an inclusive medical system based on 3000-year-old ancient texts. It incorporates varied treatment modalities, including acupuncture, acupressure, Chinese herbal medicine, meditative movements such as tai chi and qi gong, moxibustion, cupping, and specialized massage techniques referred to as tui na.

Acupuncture and TCM are based on the theory that health is determined by the balance of vital energy flow, called qi (pronounced "chi"), which is thought to be present in all living creatures. TCM utilizes concepts, such as yin/yang, dampness, and wind, which have no equivalents in conventional medicine and are therefore difficult to explain in standard medical terms. "Yin" represents the concept of cold, slow, and passive, while "yang" represents energy that is hot, fast, and active. Health is believed to be based on a balance of these and other opposing forces such as dampness and dryness and require the free flow of qi. Disease is felt to arise from an imbalance in these forces. Imbalance leads to blockage of qi (vital energy) along specified pathways, called meridians. In all organisms, qi is believed to flow through particular channels, called meridians, and TCM therapies are utilized to unblock the flow of qi. Unlike in conventional medicine, treatment plans are highly individualized and are based on an individual's constitution, as assessed by the TCM provider, as well as on their symptoms. Thus two patients with identical complaints might receive entirely unique treatment plans based on their baseline characteristics.

The acceptance of acupuncture in the United States continues to rise, with a 50% increase in use between 2002 and 2012. In that same time period, the number of United States licensed acupuncturists increased 100%.[26] Acceptance is also growing among medical educators. A survey of Pain Fellowship Directors revealed positive impressions of acupuncture in the treatment of common pain conditions. Acupuncture is often included in their treatment planning, is frequently available through the institution, and is integrated into the Fellowship curriculum.[27] Dry needling is also

increasing in popularity. It is a treatment modality that has similarities to acupuncture (thin needles inserted into trigger points) but is performed by non-acupuncturists, such as physical therapists, and does not adhere to the principles of TCM. This has caused consternation for some in the acupuncture community, while others have advocated for a collaborative approach.[28] Acupuncture points (acupoints) are located along the recognized meridians, and the process of acupuncture involves the insertion of thin needles into these points. Although meridians cannot be visualized anatomically, acupuncture points often correspond to depressions in muscles, bones, or neural foramina and may have their neurovascular bundle, which distinguishes the acupoint from surrounding tissue.[29] They are often palpable and may be tender to palpation.

From a conventional medicine point of view, the mechanism of action of acupuncture has not been unequivocally determined. Theories for acupuncture efficacy include the release of endorphins and neurotransmitters, enhanced local immune response, enhanced circulation and smooth muscle relaxation, stimulation of tissue growth and repair, and spinal and peripheral nerve stimulation. Substantial evidence supports the theory that acupuncture creates physiologic change at the site of needle insertion, in the cerebral cortex, and hormone and endorphin release.[29] It may also stimulate neurogenesis.[30] It has been shown to reduce lameness in horses[31] as well as pain and locomotion in dogs with musculoskeletal disorders,[32] suggesting effectiveness that does not rely on the placebo response.

There is abundant evidence to support the use of acupuncture in varied medical conditions, yet there are particular challenges to acupuncture research that may affect results. Acupuncture has no true placebo control, and sham acupuncture has sometimes been shown to be as effective as true acupuncture.[33] Inserting needles in "sham" acupuncture points might elicit physiologic change, and even sham acupuncture needles that press but do not puncture the skin may approximate acupressure effects if they are used at specified acupoints. In addition, standardized acupuncture treatments are often used in research to provide a consistent and replicable approach. That is, all patients with back pain would receive acupuncture at the same acupoints. However, this does not replicate the individualized treatment approach of acupuncture used in practice, thus creating a research environment that does not reflect real life conditions.

Acupuncture is used in various health conditions and is also used by those without specific symptoms to maintain optimal health. It is most commonly used for musculoskeletal pain relief. A 2001 review on acupuncture safety found that minor adverse events were common, but serious adverse events were rare. The most commonly reported adverse events were needle pain (1%–45%), tiredness (2%–41%), nausea or vomiting (0.01%–0.2%), and slight bleeding/bruising (0.03%–38%; Box 61.1). Feeling faint was very rare (0%–0.3%), and pneumothorax was extremely rare—only occurring twice in nearly a quarter of a million treatments.[34] A more recent overview of systematic reviews of acupuncture safety confirmed relatively frequent minor adverse events but rare serious ones.[35] Acupuncture is safe even in people receiving anticoagulation.[36]

Laws concerning the practice of acupuncture are defined by each state. Practitioners may include licensed acupuncturists who have completed over 1,000 hours of training at a college of Oriental Medicine or Masters level program, chiropractors who may receive some training within their professional course of study and may choose to pursue additional post-graduate training, and physicians and dentists who pursue acupuncture training after completing their professional programs. Most programs targeted to physicians, chiropractors, and dentists include approximately 200–400 hours of training. Board certification is available through the NCCAOM National Certification Commission for Acupuncture and Oriental Medicine (https://www.nccaom.org). For physicians, Board certification is available through the American Board of Medical Acupuncture (http://www.dabma.org/requirements.asp). Acupuncture styles differ and can include traditional Chinese acupuncture, five-element acupuncture, Korean or Japanese acupuncture, and auricular acupuncture. Evidence of superiority of one form over the others is not available.

• Box 61.1 Adverse Events Associated With Complementary Medicine Modalities

Treatment	Adverse Event
Acupuncture	Needle pain Tiredness Nausea/vomiting Bleeding/bruising Feeling faint Pneumothorax
Yoga	Soft tissue injury (e.g. overuse) Axial nonbony injury (e.g. degenerative joint disease (DJD) exacerbation)Bony injury (e.g. compression fractures)
Manual therapy	Increased pain Muscle stiffness Headache

A review of Cochrane reviews of acupuncture for pain found that acupuncture was effective for migraines, neck disorders, tension-type headaches, and peripheral joint osteoarthritis.[37] One well-designed randomized controlled trial of acupuncture in the treatment of knee osteoarthritis involved 507 patients recruited from two University outpatient clinics (Box 61.2).[38] The patients were randomized into one of three groups: true acupuncture, sham acupuncture, or education control. The primary measured outcomes were changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores at eight and 26 weeks. Secondary outcomes were patient global assessment, 6 minute walk distance, and physical health scores of the 36-Item Short-Form Health Survey (SF-36). Participants in the true acupuncture group experienced significantly greater improvement in WOMAC function scores than both the sham acupuncture and education groups at eight weeks but not in WOMAC pain score or the patient global assessment. At 26 weeks, the true acupuncture group experienced significantly greater improvement than the sham and education groups in the WOMAC function score, WOMAC pain score, and patient global assessment. The authors concluded that acupuncture could be used as adjunctive therapy in the treatment of knee osteoarthritis.[38]

A Cochrane review of acupuncture revealed that sham-controlled trials show statistically significant benefits; however, these benefits are small and may be due partly to placebo effects from incomplete blinding.[39] Acupuncture has been shown to be helpful in the perioperative period to decrease anxiety, and postoperative analgesic requirements,[40] and has been shown to improve chronic low back pain symptoms in some studies,[41] but not others.[42] It shows benefit in some musculoskeletal conditions, such as carpal tunnel syndrome, but no benefit in others, such as

• Box 61.2 Clinical Conditions Where Acupuncture May Be Effective

- Chronic low back pain
- Carpal tunnel syndrome*
- Migraine
- Chronic tension-type headache
- Some neuropathic conditions (Diabetic neuropathy, Bell's palsy)**
- Non-specific musculoskeletal pain
- Peripheral joint osteoarthritis, e.g. knee
- Shoulder pain

* No benefit in patella-femoral pain.
** Probably effective in HIV neuropathy.[45]
See text.

patellofemoral pain.[43] A Cochrane review of acupuncture for the treatment of chronic tension-type headaches suggested that acupuncture could be a valuable non-pharmacologic tool in patients with frequent episodic or chronic tension-type headaches.[44] It has also shown benefit in varied neuropathic conditions.[45] A recent meta-analysis evaluated the efficacy of acupuncture for non-specific musculoskeletal pain, osteoarthritis, chronic headache, or shoulder pain (Box 61.2). The primary outcome measures were pain and function. Data from 39 studies, which included more than 20,000 patients, showed that acupuncture was superior to sham as well as no acupuncture control for each pain condition.[46] Thus although the evidence suggests that acupuncture is beneficial for treating varied pain syndromes, the picture is unclear. Expectation of benefit, possible physiologic action of supposed sham controls, differing styles of acupuncture, and acupuncture research protocols that may not match the "real life" practice of acupuncture all create some uncertainty regarding the effectiveness of acupuncture for the treatment of pain. However, a mounting body of evidence suggests the benefits of acupuncture when added to conventional care and clear evidence of safety.

Mind-Body Medicine

The term mind-body medicine does not refer to a specific treatment modality; instead, it refers to a group of modalities unified by the underlying concept of an intricate connection between the mind and the body. The physical, emotional, spiritual, and social aspects of our lives impact health and wellbeing, and dysfunction in one domain can lead to dysfunction in another. Mind-body medicine asserts that the mind can positively affect the body in the pursuit of health and wellness.

Our daily experience makes it clear that the mind can affect physiology. Blushing from social embarrassment results from increased blood flow to the face, frightening movies can increase cardiovascular vital signs, and sexually stimulating visual material can increase blood flow to the penis. Similarly, psychological stress can lead to clear physiologic changes, most of which are potentially harmful. Chronically elevated blood pressure and heightened muscular tension leading to headaches or neck pain and increased incidence of chronic pain syndrome may be associated with stress. Pain and stress are interconnected, often generating a vicious cycle in which pain causes stress and subsequently stress causes more pain. Mind-body techniques can provide improved ability to cope with pain, decreased perception of pain, and an increased sense of wellbeing and relaxation. The psychological tendency to catastrophize has been associated with increased pain perception,[47] and mind-body techniques can help temper this anxious state.

The relaxation response is a physical state or reaction that counteracts the physiologic and emotional responses to stress and is essentially the opposite of the fight or flight response. It was first described by Herbert Benson and colleagues at Harvard Medical School in the 1970s.[48] Just as eliciting the stress response can generate unhelpful physiologic changes, eliciting the relaxation response can result in health inducing physiologic effects. The relaxation response is different than simply relaxing with a book or in front of the television. Although these activities may be considered "relaxing," they do not generate the physiologic changes associated with the relaxation response. The relaxation response is elicited by focusing the mind on a particular word, phrase, breath, image, or action and adopting a passive attitude toward one's thoughts. Modulation of cardiovascular parameters, muscular relaxation, and normalization of stress hormones such as cortisol, epinephrine, and norepinephrine are all associated with the relaxation response.

Mind-body techniques are varied and become easier to do with practice. Techniques include abdominal breathing, meditation, guided imagery, biofeedback, yoga, tai chi, qi gong, therapeutic arts, and even prayer. No mind-body technique is intrinsically more effective than another, and all can be used to decrease stress and elicit the relaxation response. Some involve movement and stretching, while others are practiced in seated or recumbent positions. They can be performed in groups, with an individual instructor, or alone. Patients may choose to try different mind-body techniques to find one, or several, that they prefer. Varied mind-body techniques have shown improvement in pain intensity and a suggestion of decreased need for opioids,[49] with meditation and hypnosis showing more benefit than other mind-body techniques. One challenge in the field of mind-body medicine is the lack of clarity regarding the needed "dose" of mind-body practice required for benefit. One study of a very brief (10 min) relaxation training experience did not show increased experimental pain tolerance compared to control.[50] Mindfulness Based Stress Reduction (MBSR) is a structured and standardized mind-body program that provides a large "dose" of mind-body practice. It is an eight-week training program with expectations for daily home practice. It usually requires a fee for participation. However, an online version is available at no cost (https://palousemindfulness.com). A randomized controlled trial of 342 adults aged 20–70 years with chronic low back pain found significant improvement in pain and functional limitation in those who participated in an MBSR program compared to usual care.[51] CBT was also assessed; MBSR and CBT were equally effective, and improvements persisted at 26 weeks. Similar improvements in pain, as well as the quality of life, were found for patients with chronic headaches.[52] Specific mind-body techniques are described in the ensuing paragraphs.

Progressive Muscle Relaxation

Progressive muscle relaxation is a commonly used technique for eliciting the relaxation response and relieving muscular tension. It is easy to learn and is accessible even to people who may not be familiar with or interested in meditation. It involves sequentially relaxing various muscle groups, often starting at the head and moving down the body to the feet. Participants may tense the muscle prior to relaxing it (for example, clenching the jaw and then releasing it) or simply bring their attention to a muscle group and intentionally relax it. Progressive muscle relaxation is often combined with guided imagery (see below). On its own, it has been shown to improve pain even with difficult populations such

as those with sickle cell disease.[53] It has also been used successfully to decrease headaches in children.[54] A sample progressive muscle relaxation script is provided in Appendix A.

Meditation

Moreover, 19% of the adult, civilian, noninstitutionalized United States population practices some form of meditation.[55] The term meditation refers to a broad variety of similar practices but may be quite distinct in intention. Depending on the culture and tradition of the meditator, meditation may be used to induce relaxation, increase vital energy ("qi" or "prana"), attain closeness to a deity, or induce a state of contemplation or ultimate consciousness. Many Western and Eastern religious faiths include meditative practices within their traditions, and in the past 40+ years, more secular versions of meditation have gained popularity. These forms of meditation are generally considered relaxation techniques, and they involve an intentional focus on the act of breathing, a sound, an object, a phrase, or a movement. The goal of these forms of meditation is generally to increase awareness of the present moment, elicit the relaxation response, reduce stress, and enhance personal growth.

Two common forms of meditation used in the West are MM and concentrative meditation. In MM, participants pay full attention to their breathing, focusing on each inhalation and exhalation. When thoughts, feelings, or sensations arise, the meditator simply notices and accepts them non-judgmentally and brings attention back to the breath. In concentrative meditation, attention is focused intently on one thing, such as an object (a candle) or a sound, word, or phrase, which is repeated silently with each breath cycle. Common phrases might include "peace" with inhalation and "love" with exhalation or "all will/be well."

Practicing focused attention in the present moment and nonjudgmental acceptance of experiences or thoughts decreases the mind's tendency to worry about the future or ruminate about the past. It has also been found useful in pain conditions. In one interesting study of experimental pain, subjects were taught MM, which they practiced 20 minutes daily for three days. The investigators measured pain sensitivity before and after meditation training and found decreased sensitivity after three days of meditation. The authors believed that the increased ability to tolerate pain was related to decreased anxiety and an increased ability to focus on the present moment.[56] A more recent study of 40 participants found that those assigned to a brief MM training had increased pain tolerance to experimental pain as well as a more rapid attenuation of pain intensity when compared to controls.[57] An interesting study addressed the question of whether mindfulness meditation-based analgesia is mediated by endogenous opioids.[58] The investigators performed a double-blind, randomized study of the effect of MM versus control on the impact of noxious heat while receiving either naloxone, an opiate antagonist, or saline. The meditation participants had decreased pain unpleasantness and intensity, and this effect was not negated by naloxone. This strongly suggests that the pain modulating effect of meditation is not related to endogenous opioids. A systematic review and meta-analysis of MM for chronic pain found improvements in pain, depression, and quality of life. However, the evidence was generally of low quality.[59]

Guided Imagery

Guided imagery is the generation of specific mental images to evoke a state of relaxation or physiologic change. It takes advantage of the communication links between the mind and the body and uses the imagination to generate intentional physiologic states, such as relaxation or relief of pain. It can be performed with a therapist and patient in person or by a patient alone, listening to a recording.

One study of fibromyalgia patients randomized subjects to either six weeks of daily guided imagery audiotapes or usual care. People in the guided imagery group had statistically significant improvements in their ability to cope with fibromyalgia, with a decrease in Fibromyalgia Impact Questionnaire score and increased self-efficacy for managing pain.[60] Interestingly, the imagery dose was not significantly associated with the outcome. This lack of dose-response relationship suggests that even using guided imagery infrequently might be beneficial. Guided imagery has also been shown to reduce headache intensity, duration, and frequency,[61] musculoskeletal pain,[62] and pain related to breast biopsy.[63]

Used with progressive muscle relaxation, guided imagery has been shown to reduce pain and fatigue in patients receiving chemotherapy[64] and pain related distress in terminal cancer patients.[65] There is evidence that guided imagery is helpful in the perioperative period. It has been shown to reduce the length of hospital stay[66] and decrease postoperative pain and preoperative anxiety.[67]

Hypnosis

Hypnosis involves leading the patient into a focused, trance-like state. By concentrating attention intensely on one specific thought, memory, feeling, or sensation and blocking out all distractions, patients become calm, relaxed, and open to hypnotic suggestion. Health inducing suggestions can be offered, including a decrease in anxiety or pain. Patients' free will remains intact during hypnosis, and they cannot be led against their will to perform actions that are dangerous to themselves or others.

There is evidence to support the use of hypnosis in various pain syndromes such as chronic pain, cancer, osteoarthritis, sickle cell disease, temporomandibular disorder, fibromyalgia, non-cardiac chest pain, and disability-related chronic pains.[68] A recent meta-analysis evaluating the impact of hypnosis with direct analgesic suggestion on pain showed that participants who were highly or moderately suggestible had significantly decreased pain.[69] Those who were minimally suggestible did not have a meaningful analgesic response. In a controlled study of 50 palliative care patients, those who received hypnosis had decreased pain and anxiety compared to controls, and these improvements were maintained at one and two years. The control group had a four times greater risk of increasing their pain medication usage at the two-year follow up.[70]

Yoga

Yoga originated in India but is now widely practiced worldwide and is generally used to improve relaxation, strength, and flexibility. Yoga's combined focus on mindfulness, breathing, and physical movements are health inducing for the mind and the body. Several styles of yoga are commonly practiced in the United States, including Hatha, Vinyasa, Ashtanga, Iyengar, Anusara, and Bikram, and each has unique intentions and techniques. Hatha yoga may be more appropriate for beginners, while Ashtanga yoga tends to be more physically demanding. "Power yoga" classes are appropriate for people seeking aerobic exercise, and they are often modifications of the Ashtanga style. Bikram yoga, often called "hot yoga," is practiced in a room heated to between 95 and 100 degrees, and Iyengar yoga is particularly concerned with bodily alignment.

Yoga is often used as a relaxation practice, but it has also been shown to be helpful in pain conditions. A recent Cochrane review

of yoga for chronic low back pain suggested a benefit for yoga in improving pain related function when compared to non-exercise controls.[71] These benefits persisted at three and six months. Yoga was associated with more adverse events than non-exercise controls, but none of the adverse events were serious. Veterans also showed that back pain was reduced after a yoga intervention,[72] but not all yoga studies for back pain have shown benefit.[73] Yoga has also shown benefit in chronic neck pain,[74] shoulder and arm pain in women with breast cancer,[75] chronic pelvic pain in women with endometriosis,[76] and even children with sickle cell crisis.[77] Benefits from yoga have been shown with both in person and telehealth sessions.[78]

An assessment of injuries attributed to yoga[79] found three categories of injury: soft tissue injury, axial nonbony injury, and bony injury (Box 61.1). Within the soft tissue group, overuse injuries were common. Within the axial group, exacerbation of degenerative joint disease was prominent; kyphoscoliosis, spondylolisthesis, and compression fractures were approximately equal contributors to the bony injuries. Hyperflexion and hyperextension of the spine were common causes of injury. Spinal hyperflexion may increase the risk of a compression fracture in high risk populations.[80]

Yoga therapy is an emerging field that aims to use the philosophy and practice of yoga to facilitate wellbeing, regardless of physical limitations. It focuses more on the individual than on the asanas (poses) and supports personal transformation within the experience of illness, pain, or disability.[81] A national survey of yoga therapists revealed that most yoga therapy is delivered in urban or suburban settings, and most therapists provided both therapeutic yoga classes and individual sessions. Common reasons for seeking out yoga therapy included anxiety, back or neck pain, and joint pain or stiffness.[82]

Tai Chi and Qi Gong

Tai chi and qi gong are ancient meditative movement techniques that combine standardized physical movements with meditation and relaxation breathing techniques. They have been used for thousands of years in China, and, as part of traditional Chinese medical theory, they are thought to unblock and balance vital energy ("qi"). In the United States, tai chi and Qigong are often used to relieve stress, improve balance and reduce pain. The practices use conscious, often slow, movements and focus on goals different from conventional Western exercise, such as developing consciousness within the body and enhancing the smooth flow of energy.

A recent study published in the American Journal of Public Health assessed the usage trends of tai chi/qi gong/yoga from 2002–2017 using National Health Interview Surveys. Use of these modalities, assessed collectively, increased from 5.8% in 2002 to 14.5% in 2017.[83] Stated reasons for use included the expectation that they would be beneficial, the focus on the whole person, and the fact that these modalities are "natural." The top three conditions for which people used these meditative movement modalities were acute and chronic pain, arthritis, and depression.

A systematic review and meta-analysis of tai chi for musculoskeletal pain assessed only randomized controlled trials. Fifteen trials met the inclusion criteria, and the quality of the studies was moderate. Tai chi was found to be more effective for pain and disability than no treatment or usual care.[84] Tai chi has been shown to decrease pain in fibromyalgia as effectively as aerobic exercise[85] as well as to decrease depression, improve fatigue, enhance sleep, and improve both physical and psychological quality of life in addition to improving pain.[86] It was shown to be equal to physical therapy in the treatment of knee osteoarthritis,[87] and to improve function and quality of life in this population.[88]

A review of the medical literature found significant beneficial health effects of tai chi and qi gong. The authors reviewed 77 articles reporting results of 66 randomized controlled trials, including over 6,000 patients of the health effects of tai chi or qi gong. Control groups included non-exercise controls, exercise controls, or both. The most convincing evidence for health benefits in this review was for bone density, cardiopulmonary fitness, fall prevention, balance, quality of life, and self-efficacy.[89]

Virtual Reality

Virtual reality uses computer technology to create a simulated but immersive environment. Using a head-mounted display and employing as many senses as possible, virtual reality creates three dimensional images that are highly realistic and place the participant "inside" the experience. Increasingly, virtual reality has been used in medical contexts to help manage pain and other conditions.

A recent comprehensive literature review of virtual reality for procedural pain and distress showed benefit even for patients undergoing extremely painful procedures such as wound care in burn patients.[90] It also showed benefit in cancer patients undergoing chemotherapy. Only mild side effects were observed. Virtual reality has also shown benefit in phantom limb pain,[91] acute experimental pain,[92] and in one study of morphine plus virtual reality, the combination was more effective for pain and anxiety management than morphine alone.[93] In addition to its benefit in acute and procedural pain, virtual reality has shown benefit in the management of chronic pain.[94,95]

Therapeutic Art and Music

Creative arts can be used in the therapeutic environment to relieve stress, anxiety, and pain in patients and caregivers.[96,97] Art therapy has been used to stimulate relaxation in the palliative care setting,[98] and as distraction from negative side effects of bone marrow transplant.[99]

A Cochrane review of music therapy in people with cancer assessed 30 trials for a total of 1891 participants. They included music from multiple sources, including recorded music and music provided by trained music therapists, and found that music interventions may have beneficial effects on pain, anxiety, mood, and quality of life in people with cancer.[100] Another more recent review that evaluated studies according to the Cochrane Collaboration Guidelines found similar results.[101] In addition, patients randomly assigned to music therapy plus usual care versus usual care alone after spinal fusion surgery showed a decrease in postoperative pain.[102] Music therapy has also shown reductions in pain, anxiety, and opioid use during burn dressing changes,[103] and postoperative reductions in anxiety and pain after thoracic surgery.[104] It may be more effective when the music is chosen by the patient rather than the practitioner.[105] Music therapy has been used successfully in the emergency department,[106] in the intensive care unit,[107,108] and for palliative care patients.[109]

Energy Medicine

Energy medicine modalities, sometimes called biofield therapies, are based on the idea that all living creatures have energy that can be manipulated in the pursuit of health by a trained practitioner.

A three year study of 118 chemotherapy patients investigated the role of Reiki, a form of energy medicine, in the management of anxiety, pain, and global wellness in cancer patients. Pain and

anxiety were evaluated with a visual analog scale (VAS). In the patients who received the full treatment course (4 Reiki sessions), mean VAS anxiety scores decreased from 6.77–2.28, which was a highly significant result; however, no control group was included, and significant bias was introduced. Mean VAS pain scores also decreased from 4.4–2.32, but this did not reach statistical significance.[110] A more recent meta-analysis of Reiki for pain also showed that it resulted in a statistically significant decrease in VAS pain score,[111] and it appears to have a similar pain-reducing impact in children undergoing bone marrow transplants, but rigorous studies are lacking.[112] A large scale effectiveness trial of Reiki for physical and psychological health revealed statistically significant improvements in pain, affect, fatigue, nausea, anxiety, depression, and overall wellbeing.[113]

While Reiki is likely safe and may be effective for pain and anxiety, higher quality studies are needed to solidify its clinical indications.

Manual Therapy

The term *manual therapy* is non-specific and refers to techniques that use the hands to diagnose and treat disorders of the musculoskeletal system (MSK). More specific terms include high velocity, low amplitude joint manipulation, joint mobilization, and soft tissue manipulation. These techniques are often used to treat various painful acute, subacute, and chronic musculoskeletal conditions, and multiple studies have demonstrated effectiveness.[114-122] Many studies show a significant effect on pain improvement in outcome measures, although in some cases, the effect size is small.[114,117,119,123] Spinal manipulation, one of the oldest forms of therapy for low back pain, has mostly been practiced outside of the medical profession until the latter part of the 20th century.[124] Today, manual therapy may be performed by physical therapists (PT, DPT), chiropractors (DC), massage therapists, osteopathic physicians (DO), and others and may include techniques such as chiropractic manipulative therapy (CMT), craniosacral therapy, and osteopathic manipulative techniques (OMTs). A 1991 RAND study estimated that 94% of all manipulation is performed by chiropractors.[125] While physical therapists have undoubtedly increased their utilization of this modality, it is likely that the vast majority of this therapy is still provided by chiropractors.

The evidence for the benefit of manual therapy in the treatment of patients with musculoskeletal pain continues to increase, and the risk of adverse events appears to be low; however, not all studies show clinical benefit or cost effectiveness. Non-pharmacologic pain management strategies may have both safety and cost benefits, and thus the American College of Physicians (ACP) guidelines now recommend spinal manipulation, massage, superficial heat, and acupuncture as first line options in patients with acute low back pain. A recent study by Thomas and colleagues on mild to moderate chronic low back pain in young adults compared spinal manipulation with spinal mobilization and sham cold laser (placebo). Their results showed no significant difference in change in self-reported disability scores between spinal manipulation, spinal mobilization, and placebo.[126] Thus it is not yet completely clear which manual medicine interventions may be most effective and if patients with greater pain related disability may benefit more or less than those who are less affected. Non-pharmacologic approaches are associated with reduced harm compared to pharmacologic approaches.[127] Therefore further research on the potential benefits of manual therapy approaches may benefit both patients and healthcare systems. Of note, the ACP guidelines state that providers should administer physical therapies with appropriate training, such as osteopathic physicians, chiropractors, and physical therapists. The Lancet reports similar European guidelines for the management of low back pain.[128]

A systematic review of randomized clinical trials of manual therapies evaluated the evidence for spinal manipulation or mobilization in treating several different conditions, including 13 musculoskeletal conditions and headaches. The authors reviewed 49 systematic reviews, 16 evidence-based clinical guidelines, and an additional 46 randomized clinical trials not yet included in systematic reviews and guidelines. They found spinal manipulation to be effective in adults for acute, subacute, and chronic back pain, migraine and cervicogenic headache, and cervicogenic dizziness, and thoracic manipulation or mobilization was determined to be effective for acute and subacute neck pain.[119] Other conditions that are reported to respond to manual therapy are costosternal pain,[129] lumbar spinal stenosis with neurogenic claudication,[130] pelvic girdle pain,[131] pain in extremity joints,[132,133] osteoarthritis,[134] and myofascial pain. Although anecdotally reported, the benefit of manual therapy for temporomandibular disorders and orofacial pain is unclear.[135]

Modern society continues to struggle with an opioid abuse crisis of epic proportion. A growing body of research demonstrates that MSK pain patients referred to or self-refer to practitioners of manual therapies have a lower likelihood of filling an opioid prescription than those seeking conventional care,[136-142] in some cases as much as a 60% reduction.[137]

Significant healthcare cost savings are realized using manual therapy practitioners: 2012 Optum Data for risk adjusted total episode cost by entry point for 1.4 million nonsurgical episodes of low back pain revealed that patients starting care with manual therapy providers (in this case, chiropractors) is the most common entry point and has the lowest cost per episode, including a 50% reduction in imaging costs.

Several models attempt to explain the mechanisms by which manipulation or manual therapy modulates pain and improves function. There are three primary models:

Structural model: States that misaligned structures, such as bones out of place, impinge on nerves and stress soft tissues, thereby stimulating nociceptors. Common terminology includes "subluxation," "osteopathic lesion," "pelvic obliquity," "leg length inequality," and "torsion." It is believed that correction of these misalignments via manual methods eliminates pain and improves function. The evidence base does not support the concept that structural misalignments are clinically significant in most instances, and the premise that manipulation or mobilization can correct structural misalignments has been largely disproven.[143-145]

Functional model: Muscular imbalance leads to abnormal joint loading, which in turn causes loss of joint function at the level of accessory motion, also termed "joint play."[146–148] Terminology includes "somatic dysfunction," "biomechanical lesion," "blockage," "fixation," "restriction," "muscular inhibition/facilitation," and "instability/stabilization." Syndromes include upper and lower crossed syndromes,[149,150] each characterized by specific patterns of muscular facilitation (tightness) and inhibition (weakness). For example, upper crossed syndrome is characterized by facilitation or "tightness" of the upper trapezius, levator, sternocleidomastoid, and pectoralis muscles, whereas the deep cervical flexors, lower trapezius, and serratus anterior muscles are inhibited and weak. Practitioners use a combination of manipulation and rehabilitative exercise with the intention of changing muscle activity and reducing nociceptive input. This is the current model presented

in most chiropractic, physical therapy, and osteopathic manual therapy programs.

Neurophysiologic model: This model is consistent with the emerging concept that the pain experience is a central nervous system output that is modulated by multiple factors such as stress, anxiety, fear avoidance, experience, and context in the brain's "neuromatrix."[151] Wellens and others proposed that manual therapy introduces a novel stimulation into the central nervous system that may help the brain downregulate the perceived threat of nociceptive stimuli, thereby decreasing the pain by descending inhibition and other peripheral and central mechanisms. This, in turn, may stimulate a change in the maladaptive motor responses produced by the brain in response to pain. Other reflexive reactions at the spinal cord level may affect temporal summation and downregulate the value (threat) of the nociceptive input even more.[152,153]

Bialosky et al.[154] propose that manual therapy affects the pain state by

- decreasing peripheral inflammation and nociception
- deceasing activation/temporal summation at the spinal cord level
- activating descending modulation via the brain and central nervous system

Even though this model is hypothetical, there is an impressive body of supportive literature.[155–158] Some of these studies describe neurophysiologic changes following spinal manipulation, including neuroplastic changes, alteration in motor neuron excitability, and increase in cortical drive. High velocity, low amplitude manipulation (HVLA) resulting in an audible "pop" or cavitation has been shown to down regulate the sensitivity of muscle spindles and/or other segmental sites of the 1a stretch reflex pathway.[159] Research by Reed in 2015 found that HVLA manipulation decreased sensory input from the paraspinal muscle spindles.[160]

Practitioners of manual therapy generally believe that musculoskeletal problems arise from abnormal repetitive movement patterns, prolonged static posture, trauma, lack of exercise, inadequate diet, and poor lifestyle choices, leading to diminished capacity and excessive and/or asymmetric musculoskeletal loads creating nociceptive input and impairing function. Examples of musculoskeletal asymmetry that can lead to painful conditions include chronic elevation of one shoulder when carrying a heavy purse, abnormalities in tissue mobility after prolonged immobilization, and forward head carriage associated with desk work, computer use, and prolonged sitting causing soft tissue overload.

The forms of manual therapy most frequently employed in clinical practice are manipulation and mobilization.

Manipulation (also called high velocity, low amplitude, or thrust manipulation) is the skilled introduction of a rapid rotational, shear, or distraction force via a thrust or impulse to an articulation, frequently associated with an audible popping sound caused by instantaneous joint cavitation.

Mobilization is a slower, deliberate process of articular movements of the joint intended to relieve pain, improve biomechanical elasticity, and enhance range of motion. It can be passive or actively assisted by the patient.

Soft tissue manipulation or mobilization is direct pressure, transverse friction massage, manual stretching, instrument assisted soft tissue mobilization (IASTM) with or without passive or active motion that seeks to relieve pain and improve function by "releasing" trigger points, mobilizing fascia, and reducing entrapment of peripheral nerves. The Graston technique is an example of a widely used IASTM technique. Active release is a manual technique coupled with active motion by the patient to address myofascial restrictions and relieve pain. An excellent description of peripheral neurodynamics, along with exercises and techniques to address entrapped peripheral nerves, is found here.[161]

Myofascial pain syndrome is a chronic musculoskeletal pain condition with a poorly defined and complex pathophysiology. It may emerge after tissue injury, chronic stress-related muscular contraction, or excessive strain on a muscle, tendon, or ligament. Tender regions of hyperirritable, contracted muscle fibers, called trigger points, may form in the affected muscle group and cause local and referred pain. Myofascial trigger points are palpable, tender nodules within the skeletal muscle that have characteristic referred pain patterns and physiologic activity that are different from those in normal muscle tissue.[162] Emerging research suggests that painful myofascial trigger points may be initiated by neurogenic mechanisms secondary to central sensitization and not necessarily by local injury.[163] Trigger points may be treated with physical therapy, manual or IASTM, massage, transcutaneous electrical stimulation, therapeutic ultrasound, selective voluntary contraction of antagonist muscles or muscle groups,[164] injection of saline or local anesthetic medications, dry needling, or application of vapor coolant spray combined with focused muscular stretching. Botulinum toxin has also been used.[165]

For some conditions such as chronic low back pain, manipulation appears to yield a greater effect, while mobilization and soft tissue manipulation may be more well tolerated in acute pain states or more delicate structures.

Adverse Effects From Manual Therapy

Walker[166] performed a randomized controlled trial including 183 adults, aged 20–85 years, with spinal pain. His team found that common adverse events following manual therapy are frequent but minor. They included increased pain, muscle stiffness, and headache. The relative risk was not significant for adverse event occurrence, and no serious adverse events were reported. Swait concluded that existing literature indicates that benign adverse events following manual treatments to the spine are common, while serious adverse events are rare.[167]

Some case reports claim that massage and manipulation of the lumbar spine can cause lumbar disc herniation (LDH).[168] However, a 10 year population-based self-controlled case series study concluded that while a strong positive association between acute LDH and both chiropractic and primary care visits exists, there was no evidence found of excess risk for acute LDH with early surgery associated with chiropractic compared with primary medical care.[169]

Some have expressed concern that manipulation of the neck increases the risk for cervical artery dissection (CAD) stroke. A large Canadian study that included more than 100 million person-years showed that these concerns are likely unfounded.[170] although debate on this topic persists.[171,172] A recent systematic review and meta-analysis of chiropractic manipulation and CAD conducted jointly by the Departments of Neurosurgery at Penn State Hershey Medical Center and Johns Hopkins University School of Medicine concluded: "There is no convincing evidence to support a causal link between chiropractic manipulation and CAD."[173] However, there are clear contraindications to manipulative therapy (Box 61.3).[174]

Massage

Massage is a widely used form of manual therapy that utilizes varied techniques applied to the muscles, ligaments, tendons, and related structures in the pursuit of pain relief, health, and wellness.

• Box 61.3 Contraindications to Manipulative Therapy

Relative Contraindications	Absolute Contraindications
Acute disc herniation	Unstable os odontoideum
Osteopenia	Healing fracture/dislocation
Spondyloarthropathy	Avascular necrosis
Anticoagulant medication	Bone infection
Bleeding/clotting disorder	Segmental instability
Psychological overlay	Cauda equina syndrome
Hypermobility/ligamentous laxity	Large abdominal aortic aneurysm
	Referred visceral pain
	Long term repeated manipulation with symptom relief lasting <1 day
	Recognized secondary gain or malingering

Massage may be performed with the hands, elbows, forearms, or feet, as well as with appliances such as warmed stones. There are many types of massage, each with unique techniques and goals, such as Swedish massage, trigger point massage, reflexology, and lymphatic drainage.

Massage is often used to address pain syndromes such as back pain, neck pain, and sports injuries, as well as to aid in stress reduction and generation of the relaxation response. It has been found to improve symptoms of osteoarthritis of the knee[175] and chronic low back pain, decrease medication use and medical costs,[176–178] and decrease the perception of cancer pain.[179]

It is not clear whether some forms of massage are superior to others or if the benefits of varied massage styles are equivalent. One recent study randomized 401 patients with non-specific low back pain to relaxation massage, structural massage, or usual care and assessed their symptoms with the Roland Disability Score and the Symptom Bothersome Score. Participants were blinded to the type of massage but not to massage versus usual care. Both massage groups had statistically significant improvements in both outcome measures at 10 weeks compared with those receiving usual care.[180] Cost effectiveness of massage therapy for pain management in the long term has not been established. Massage is generally safe for healthy populations. Contraindications include the presence of metastatic lesions, severe osteoporosis, thrombosis, infections or wounds, active inflammatory conditions, and bleeding disorders.

Chiropractic Manipulation

Doctors of Chiropractic (DC) focus primarily on the interaction between the structure and the function of the body, with particular attention paid to the spine. Historically, the primary goal was to correct musculoskeletal misalignments (subluxations) to relieve nerve pressure and thus alleviate pain and improve the body's innate self-healing capability. The primary modality of CMT is high velocity, low amplitude (HVLA) thrust manipulation (spinal adjustment). Adjustments generally involve the use of the hands or a device to apply an intentional, controlled, rapid force to a joint or body segment thought to have impaired alignment or restricted motion. Restored intersegmental motion or joint position is believed to improve both function and general health. Modern chiropractors reject the misalignment/subluxation hypothesis instead of focusing on restoring joint mobility. There are multiple chiropractic techniques, each with its own unique set of diagnostic and treatment protocols. Some use minimal force, whereas others use a more intense force. The most common technique encountered is termed "diversified" and encompasses HVLA maneuvers for all joints of the spine and extremities. Currently, no one technique is considered superior. In addition to manual therapies, chiropractors may incorporate pain education, ergonomic modification, relaxation techniques, dietary guidance, nutritional supplementation, physical therapy modalities, and rehabilitative exercise into their treatment plans. The combination of HVLA manipulation and rehabilitative exercise appears to provide the best outcomes.[181]

Most patients who choose chiropractic care do so because of back and neck problems. Patients are generally satisfied with their chiropractic care.[182] A 2018 study by Lisi et al. investigating integrating chiropractic care into private sector medical facilities concluded that delivery of chiropractic services, including CMT, was perceived to have high value among patients, medical providers, and administration. Patient clinical outcomes, patient satisfaction, provider productivity, and cost offset were identified as markers of clinic success.[183]

In a study by Goertz et al., 91 patients were randomized to either "standard care" or "standard care plus chiropractic care" (CMT). The authors concluded that "CMT in conjunction with standard medical care offers a significant advantage for decreasing acute low back pain and improving physical functioning compared with only standard care."[184]

Osteopathic Manipulation

Osteopathic medical education is similar to that found in allopathic medical schools, with the added focus on a holistic and preventive approach to medicine. In addition, osteopathic physicians learn OMT, which is not included in the allopathic medical school curriculum. OMT is a hands-on practice that attempts to restore normal musculoskeletal movement and function and decrease pain.

Osteopathic physicians may choose any specialty and can earn board certification from both osteopathic and allopathic medical boards. Most osteopathic physicians complete allopathic residencies and practice indistinguishably from allopathic physicians; however, some others focus their practice on osteopathic principles and techniques.

Osteopathic principles include working in partnership with patients to facilitate wellness and prevent disease and the concept that structure influences function. That is, a structural problem in one part of the body may affect function in that region and possibly others. Osteopaths generally believe that the body has an innate ability for self-healing, and OMT techniques are thought to support this process.

OMT procedures are directed at increasing mobility in restricted areas of musculoskeletal function and reducing pain. Some practitioners focus on pain relief, whereas others are more interested in the influence of increased mobility within the musculoskeletal system. The stated goal of OMT is to restore maximal, pain-free movement of the musculoskeletal system in postural balance.[185] Techniques include muscle energy technique, mobilization with and without impulses, indirect technique, myofascial release, and integrated neuromusculoskeletal technique.[185]

OMT has been demonstrated to be effective for neck pain[185] and migraine headache symptoms, with pain intensity, functional disturbance, and days of disability all showing improvement compared with control. A systematic review and meta-analysis of OMT for low back pain concluded that OMT significantly reduces low back pain symptoms, with the effect lasting at least three months.[186]

Orthopedic Manual Physical Therapy

Orthopedic manual physical therapy is the name given to manual therapy as practiced by physical therapists.[187,188] Manual therapy is part of the core physical therapy curriculum, with most practitioners gaining knowledge and skills through continuing education or fellowships.[188] Physical therapists trained in manual therapy use techniques such as stretching, mobilization, and muscle energy-related techniques to increase range of motion, improve function, modulate pain, decrease tissue inflammation, and facilitate tissue repair. Rehabilitative exercise and other physical therapy modalities such as electrical muscle stimulation and therapeutic ultrasound are also used.

Practitioners of manual medicine may be trained as physical therapists, osteopathic physicians, chiropractors, and to some extent, massage therapists, and strict distinction between practice styles and techniques is lacking. A standardized knowledge base with certification available to all relevant practitioners would be valuable. It is not clear whether one profession will eventually "own" manual medicine or whether a new specialty will emerge. One suggested model is to offer fellowships in manual medicine with board certification that would be available to physical therapists, chiropractors, osteopathic physicians, allopathic physicians, and massage therapists. A program designed to enhance competency as a primary contact practitioner who manages spine related disorders has recently been launched at the University of Pittsburgh. (https://www.psp.pitt.edu/index.html). The Primary Spine Practitioner certification program is open to chiropractors and physical therapists. From the program description: "The PSP functions as primary contact provider for patients with spine related disorders (SRDs). This involves taking responsibility for managing most patients without the need for special tests or specialist referrals. It also involves identifying the minority of patients who do require further diagnostic evaluations (X-ray, MRI, CT, EMG) or specialized interventions (injections, surgery). Further, the PSP serves as an inter-professional care coordinator, referring patients for the appropriate test or specialty service and following up after these referrals to continually guide the patient toward resolution of the SRD. To perform this role, the PSP requires a very specific and refined skill set."[189]

Manual Medicine and the Biopsychosocial Model

A role that a practitioner of manual medicine may find themselves in is that of a mechanic, with the MSK pain patient believing that the provider can come to the rescue and "fix" their problem without their active participation. The locus of control over the pain becomes assigned to the practitioner, and the patient may become dependent on the practitioner to experience a decrease in pain or pain related disability. This thinking reinforces the patient's view that they are "broken" or inadequate in some way and thus must rely on the practitioner to repair their issue or dysfunction. This may reinforce fear avoidance beliefs or catastrophizing, both potent contributors to central sensitization and chronic pain. While it is true that spinal manipulation may often rapidly relieve pain, the effects are usually short lived. The analgesic effect resulting from manipulation can provide a window of opportunity to empower the patient, aiding them in discovering their own resilience by showing them how they can restore impaired physical performance, reduce their disability,[153] and regain independence.

This can be achieved particularly for the chronic pain patient, with a powerful concurrent application of manual therapy with an appropriately dosed, well-designed rehabilitation program that includes pain education. Through appropriate patient education regarding the biopsychosocial aspects of pain, including information on the nocebo response, interpretation of actual or perceived threat, fear avoidance, catastrophization, and the use of exercise to illustrate to the patient their abilities, the skilled manual therapy practitioner can collaborate with other members of the pain management team to guide the patient to discover enhanced levels of function, fitness, and empowerment. This approach guides the patient to become the primary agent in their recovery.

Homeopathy

Homeopathy is based on the principle that the efficacy of a remedy is increased as the dose is decreased. Homeopathic remedies are serially diluted, often until the remedy no longer contains any molecules of the original medication. The diluent, often water, is thought by homeopaths to be "imprinted" by the original substance, thus imparting therapeutic efficacy. Homeopathy is used by 2% of the United States population, primarily for ear, nose and throat (ENT), musculoskeletal, and respiratory complaints.[191] Its use is much more common, as high as 35%, in the German population.[191] Rigorous clinical trials and systematic analyses of the research on homeopathy have concluded that there is no evidence to support homeopathy as an effective treatment for any specific condition.[192] Similarly, a Cochrane review of homeopathy for irritable bowel syndrome could not draw a conclusion about efficacy.[193] Although high quality research validating the efficacy of homeopathy is lacking, some small studies have shown benefit in conditions such as joint pain in breast cancer patients,[195] pelvic pain,[195] and other varied chronic conditions.[196] One double-blind, randomized controlled trial of homeopathy in rheumatoid arthritis showed that it was the homeopathic consultation rather than the remedy itself that led to positive outcomes.[197]

Biologically Based Products: Herbs, Nutraceuticals, and Nutritional Supplements

A large body of clinical evidence supports the usage of biologically based products for the alleviation of pain. This supportive evidence for pain reduction spans a wide variety of herbs, nutraceuticals, nutritional supplements, and food-derived topical products. The following products have the strongest evidence supporting their usage in the reduction of pain.

Capsaicin

Capsaicin is derived from chili peppers of the genus Capsicum, which includes the cayenne pepper commonly used in cooking. Topical application of creams and gels ranging from 0.025%–8% capsaicin concentration is utilized to provide pain relief. The primary mechanism through which capsaicin is believed to reduce pain is the depletion of substance P, a neuropeptide involved in the transmission of pain signals from nerve endings to the brain and the activation of inflammatory cytokines in joints. Thus capsaicin is involved in the neuronal modulation of pain.[198]

Many high quality, randomized, double-blinded, placebo-controlled trials have found that topical application of capsaicin is an effective treatment for osteoarthritis pain. A recent literature review found that capsaicin safely reduced osteoarthritis pain of

the hand, knee, hip, and shoulder compared to placebo.[199] Motivated by the relatively common sensation of burning experienced at higher concentrations, a trial assessed the topical application of capsaicin at a concentration of 1.25% in 100 patients with osteoarthritis of the knee.[200] Capsaicin at this lower concentration was effective at improving pain. While a mild burning sensation was common, no participants dropped out of the study for this reason. Consequently, lower concentrations of topically applied capsaicin appear to be another effective treatment option for mild to moderate osteoarthritis pain.

While most capsaicin research has focused on osteoarthritis pain, several studies have assessed its efficacy for neuropathic pain.[201–203] Transient application of a dermal patch containing 8% capsaicin has been shown to be an effective option for reducing neuropathic pain. In patients with painful diabetic peripheral neuropathy, a single 30 minute application of the 8% dermal patch provided 12 weeks of pain relief compared to a placebo.[204] It was non-inferior to oral pregabalin with a faster onset and greater treatment satisfaction. Following application, capsaicin causes increased sensitivity that, with repeated use, leads to reduced sensitivity and ultimately desensitization. The 8% capsaicin patches were developed to rapidly achieve desensitization and improve compliance and tolerability. The patch is generally administered in a physician's office; it is not prescribed for home use. The patch is applied for 60 minutes after application of a topical anesthetic to decrease patient discomfort. Occasionally an ice pack or other analgesic may be necessary. Treatment may be repeated every three months. A high quality Cochrane systematic review confirmed the benefit of high concentration capsaicin patches for peripheral neuropathy of varied etiologies.[205] The observed efficacy is similar to oral agents such as pregabalin, duloxetine, and gabapentin, with fewer adverse events.[206]

Boswellia Serrata

Extracts of the Boswellia serrata plant have been used as an important component of Ayurvedic medicine for thousands of years. Western science has validated the traditional usage of Boswellia serrata for pain as its extracts elicit powerful anti-inflammatory activity through its inhibition of the 5-LOX enzyme. Several forms of Boswellia serrata have been studied and used clinically.

A double-blind, placebo-controlled study of Boswellia for patients with osteoarthritis showed that Boswellia significantly improved pain, stiffness, and physical functioning compared to placebo.[207] It also reduced the levels of C-reactive protein, an inflammatory marker. No serious adverse events were reported. Boswellia is sometimes used alongside Curcumin, and the combination may be more effective than Boswellia alone.[208]

Glucosamine and Chondroitin

Numerous meta-analyses have determined that glucosamine, either combined with chondroitin or alone, is an effective treatment for osteoarthritis pain.[209–212] Despite the abundance of positive evidence for glucosamine and chondroitin, the large glucosamine/chondroitin arthritis intervention trial found mixed results which are often misinterpreted.[213] This five-arm trial compared glucosamine alone, chondroitin sulfate alone, glucosamine/chondroitin sulfate, and celecoxib to placebo. Participants in the glucosamine/chondroitin group did not demonstrate a statistically significant improvement compared to placebo in the primary outcome (20% improvement in WOMAC pain score) of the overall study sample of patients with osteoarthritis of the knee (mild [n = 1229] versus moderate to severe [n = 354]). However, 67% of the overall study sample in the glucosamine/chondroitin group experienced at least a 20% improvement in pain with a trend toward statistical significance (P = 0.09). The lack of statistical significance at P = 0.05 was thought to be because of the unexpectedly high improvement in the placebo group (60.1%). Furthermore, among the 354 participants with moderate to severe osteoarthritis of the knee, 79% of those in the glucosamine/chondroitin combination group experienced at least a 20% improvement in WOMAC pain score, which was statistically significant when compared to placebo (P = 0.002). Interestingly, participants with moderate to severe arthritis pain in the celecoxib group did not demonstrate a statistically significant improvement compared to placebo, a rarely reported finding. While a statistical comparison between the glucosamine/chondroitin and celecoxib groups was not reported in the paper, glucosamine/chondroitin was shown to be more effective than celecoxib in patients with moderate to severe osteoarthritis.

More recently, a multicenter randomized, double-blind non-inferiority trial of combined glucosamine and chondroitin versus celecoxib for knee osteoarthritis found comparable efficacy in reducing pain, stiffness, joint swelling/effusion, and functional limitation after six months. Adverse events were mild and similar between the groups.[214] While the findings from the greater than 50 randomized controlled trials of glucosamine/chondroitin for osteoarthritis pain have not been universally positive, consideration of the body of evidence suggests that glucosamine/chondroitin is a safe and at least moderately effective treatment for osteoarthritis pain. A daily dose of 1,500 mg glucosamine and 1,200 mg chondroitin has been studied most frequently and is the typical recommended dosage.

S-adenosyl-methionine (SAM-e)

The reduction of joint pain provided by SAM-e was first observed as side effects in clinical trials for depression. Produced from L-methionine and adenosine triphosphate, SAM-e is a methyl donor involved in a wide variety of metabolic processes. Although the mechanism of action is not completely understood, SAM-e has been shown to possess anti-inflammatory and analgesic effects without causing gastrointestinal damage in animal models. SAM-e has also demonstrated chondroprotective effects through the stimulation of chondrocytes and the subsequent increase in cartilage production.

A meta-analysis of 13 clinical trials revealed that SAM-e is comparable to ibuprofen and superior to placebo in reducing osteoarthritis pain.[215] A large randomized controlled trial published subsequent to this review compared the efficacy of SAM-e to celecoxib in patients with osteoarthritis pain.[216] This study found that SAM-e was as effective as celecoxib in relieving pain after 16 weeks of treatment. In one more recent study of mice with experimentally induced nerve injury, SAM-e attenuated sensory and cognitive symptoms compared to placebo saline. The authors postulated that the symptom improvement might be partly because of the modulation of DNA methylation in the central nervous system.[217] SAM-e has also been shown to attenuate morphine tolerance in rats.[218]

More high quality human trials are needed to confirm the benefit of SAM-e for joint pain. However, since it is more often used for depression, which can exacerbate pain, it should be considered for patients with coexisting pain and depression. The onset of pain relief is slower with SAM-e than some pharmacologic pain relievers, but it has no known side effects. Most clinical trials to date have used a daily dosage of between 400 and 1,600 mg.

Omega-3 Fatty Acids

Dietary omega-3 fatty acids, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), can interrupt the production of inflammatory compounds such as the prostaglandins E2 and LTB4, interleukin-1 beta (IL-1β), leukotriene B4, and tumor necrosis factor-alpha (TNF-α). Omega-3 fatty acids also inhibit the platelet-activating factor synthesis pathway, the cyclo-oxygenase pathway, and the 5-lipoxygenase pathway. As such, omega-3 fatty acids are known to play an important role in modulating the inflammatory cascade and the pathophysiology of autoimmune conditions. Chief among the conditions impacted by omega-3 fatty acids is rheumatoid arthritis.

Omega-3 fatty acids have been shown in numerous systematic reviews to reduce the pain and joint tenderness of rheumatoid arthritis.[219–221] Multiple studies have also found that omega-3 supplementation can reduce disease-related markers,[222,223] as well as dependence upon nonsteroidal anti-inflammatory drugs and antirheumatic drugs.[224–226] In addition to reduction of the pain associated with rheumatoid arthritis, omega-3 fatty acids have also been determined to be effective in reducing neck and back pain,[227] neuropathic pain,[228] and the pain from inflammatory bowel disease and dysmenorrhea.[229] It also reduced postoperative pain and postoperative C-reactive protein, a marker of inflammation,[230] and showed benefit in the prevention and treatment of oral mucositis in patients receiving chemotherapy.[231] In obese but not non-obese patients, omega-3 fatty acids were found to reduce the arthralgias caused by aromatase inhibitors when compared to placebo.[232] No significant toxicities have been associated with the use of omega-3 fatty acids, although patients on anticoagulant medications should be mindful of the potential for interaction.

The omega-3 fatty acids EPH, DHA, and ALA are not produced endogenously in human beings and must be obtained through the diet. Dietary sources of omega-3 fatty acids include salmon, sardines, and other cold-water fish, fish and krill oils, and plant oils from flaxseed or walnuts. While all forms of omega-3 fatty acids are important, EPA and DHA have direct anti-inflammatory effects and are more easily utilized by the body.[233] Conversion from ALA to EPA and DHA is poor, particularly in men.[234] As such, the optimal forms of omega-3 fatty acids taken for therapeutic purposes in pain conditions are EPA and DHA. Accordingly, most studies to date have investigated the effects of fish oils because of their high concentration of EPA and DHA. These studies show that a minimum daily dosage of 3 g of EPA and DHA is required for clinical efficacy in pain conditions. Benefits for pain generally become apparent after at least several weeks.

Summary

An integrative approach to the treatment of pain that incorporates complementary medicine approaches into the care plan can provide clinical benefit with minimal additional risk. Understanding the mind-body connection and its relevance to pain perception and treatment is important for the care of patients with acute and, especially, chronic pain. Biologically active products, mind-body therapies, and manipulative and body-based treatments can benefit patients with some pain conditions. Energy medicine and homeopathy have minimal and low quality evidence of benefit. Integrative medicine approaches have gained greater acceptance in healthcare. Still, further large, well-designed studies of diverse complementary medicine modalities are needed to confirm which modalities are best suited to which conditions.

Key Points

- Integrative medicine is a philosophy of care that integrates conventional medical approaches with complementary modalities.
- Commonly used complementary modalities include dietary supplements, yoga, meditation, acupuncture, and massage.
- The perception of pain is multifactorial, with nociceptive and affective components, which supports the use of an integrative approach.
- Psychosocial variables, including catastrophizing and negative affect, impact the severity and chronicity of pain.
- Acupuncture has shown benefit in migraines, neck disorders, tension-type headaches, and peripheral joint osteoarthritis.
- Mind-body modalities, such as meditation and guided imagery, are safe and effective modalities that have been shown to decrease pain.
- Yoga has shown benefit in the management of multiple pain syndromes, including low back pain, chronic neck pain, chronic pelvic pain, and sickle cell disease.
- Manual medicine approaches such as massage, chiropractic, physical therapy, and osteopathic manipulation have been shown to improve pain syndromes such as low back pain, myofascial pain syndrome, and arthritis.
- Nutritional supplements may have some benefit in the treatment of pain, particularly pain with an inflammatory component.

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The references for this chapter can be found at ExpertConsult.com.

Appendix A

Find a comfortable position where you will not be interrupted. You may sit up or lie down, however you are most comfortable.

You will be focusing your attention on your body for the next few minutes. If your mind wanders, simply bring your attention back to your body.

Take a deep breath into your abdomen, trying to push your belly button out as you breathe in. Hold your breath for a few seconds, and then slowly breathe out. Take another deep breath, trying to push out your belly button as you take in a healing breath… Hold for a few seconds… then slowly release your breath.

As you exhale, imagine the tension in your body being released and flowing out of your body. And again, inhale… hold… and exhale. Feel your body beginning to relax.

Now tighten the muscles in your forehead by raising your eyebrows as high as you can. Hold for about five seconds. Moreover, abruptly release feeling that tension fall away.

Pause for about 10 seconds.

Now smile widely, feeling your mouth and cheeks tense. Hold for about 5 seconds, and release, noticing the softness in your face. Now just breathe slowly for about 10 seconds, feeling your face relax more and more with each breath.

Next, tighten your eye muscles by squinting your eyelids tightly shut. Hold for about 5 seconds, and release.

Pause for about 10 seconds, breathing slow, relaxing breaths.

Now lift your shoulders up as if they could touch your ears. Hold for about 5 seconds, and quickly release, feeling their heaviness. Pause for about 10 seconds, feeling your arms getting heavy and warm as you continue to breathe slow, relaxing breaths.

Tense your upper back by pulling your shoulders back, trying to make your shoulder blades touch. Hold for about 5 seconds, and release.

Pause for about 10 seconds, breathing slow, relaxing breaths.

Tighten your chest by taking a deep breath in, hold for about 5 seconds, and exhale, blowing out all the tension.

Breath in…and out. In…and out.

Let go of all the stress In…and out.

Now, tightly, but without straining, clench your fists. Hold for about 5 seconds, and release.

Pause for about 10 seconds.

Now, flex your biceps. Feel that buildup of tension. You may even visualize that muscle tightening. Hold for about 5 seconds, and release, enjoying that feeling of limpness. Breathing slowly in…and out.

Now tighten your triceps by extending your arms out and locking your elbows. Hold for about 5 seconds, and release. Pause for about 10 seconds, imagining that all your stress and tension is leaving your body through your fingertips.

Now tighten the muscles in your abdomen by sucking your abdomen in. Hold for about 5 seconds, and release. Pause for about 10 seconds breathing slowly deep into your abdomen, noticing your belly button moving away from your body with each inhale.

Gently arch your lower back. Hold for about 5 seconds, relax. Pause for about 10 seconds.

Feel the limpness in your upper body letting go of the tension and stress, hold for about 5 seconds, and relax. Your arms are heavy and warm… the tension is leaving your body through your fingertips.

Tighten your buttocks. Hold for about 5 seconds…, release, imagine your hips falling loose. Pause for about 10 seconds, breathing slow, relaxing breaths.

Tighten your thighs by pressing your knees together. Hold for about 5 seconds…and release.

Pause for about 10 seconds.

Now flex your feet, pulling your toes toward you and feeling the tension in your calves. Hold for about 5 seconds, and relax, feel the weight of your legs sinking down. Pause for about 10 seconds.

Curl your toes and tense your feet. Hold for about 5 seconds, release. Pause for about 10 seconds.

Now imagine a wave of relaxation slowly spreading through your body, beginning at your head and going all the way down to your feet.

Breathe in…and out…in…out….in…out.

Adapted from *The Anxiety & Phobia Workbook*, by Edmund J. Bourne

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Patient Education and Self-Management

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The 2011 report from the United States Institute of Medicine concluded that pain care should be tailored to each person's experience and that *self-management* should be promoted as a central strategy to improve care.[1] The importance of self-management was again emphasized in the National Pain Strategy (NPS),[2] a blueprint for delivering optimal pain care, and in the Centers for Disease Control Guidelines for Prescribing Opioids for Chronic Pain,[3] the Healthy People 2020 report,[4] and within the Federal Pain Research Strategy.[5] The use of self-management for chronic pain management is also recommended in several clinical practice guidelines.[6–8] Despite these broad recommendations, self-management for pain is still not routinely implemented in clinical practice. This chapter reviews the current status of pain self-management in two sections. The first section defines pain self-management, identifies its components, and provides evidence of its efficacy. The second section addresses the use of self-management in the context of primary care and describes considerations for implementation, including face-to-face and digital options, as well as guided and unguided formats. The chapter concludes with future considerations for more broad scale implementation of pain self-management into routine clinical pain management pathways.

Pain Self-Management: Definition and Components

Definition

Pain self-management (i.e. self-care) can be highly beneficial but suffers from a bad reputation. Patients and clinicians alike often misinterpret the term "self-management" to reinforce perceptions that (1) the pain being experienced is not real and therefore "real" pain treatment (e.g. medications, surgery) will not be offered, (2) the clinician is abandoning the patient to deal with the pain on his/her own, or (3) the clinician is withholding "real" pain treatment out of fear of addiction and potential liability. Factually, none of these scenarios reflect the accurate use of or the clinical potential of pain self-management. A definition may prove helpful:

> *"Self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and [lifestyle] changes inherent in living with a chronic condition. Efficacious self-management encompasses the ability to monitor one's condition and to effect[sic] the cognitive, behavioral and emotional responses necessary to maintain a satisfactory quality of life. Thus, a dynamic and continuous process of self-regulation is established."*[9]

Self-management refers to all the things that a person can do on his/her own to address pain beyond visits to a health professional (which may be frequent or not at all). It does not replace traditional medical care but supplements current practices and bridges the gap between healthcare visits. One might think of pain self-management in the same way as one thinks about self-management for diabetes (e.g. lifestyle changes, dietary changes, monitoring glucose). For diabetes care, these behavioral changes do not replace medical management; they facilitate greater functioning and quality of life as an integral part of health care for a chronic condition.

Components of Pain Self-Management

Pain self-management programs (SMPs) share several key components. The most commonly featured components are[10,11] (1) functions of the patient-clinician relationship (e.g. shared decision making, patient education, goal setting, and action planning), (2) building self-efficacy (e.g. skill building, problem solving, and personalized tailoring), (3) self-monitoring (e.g. symptom monitoring and behavioral monitoring) and (4) social support (e.g. relationship maintenance and cultural considerations). Each component will be briefly described (Table 62.1).

TABLE 62.1 Components of Pain Self-Management Programs

Functions of the Patient-Clinician Relationship	Pain Education Shared Decision Making Goal Setting Action Planning
Self-Efficacy Building	Skill Building Problem Solving Personalized Tailoring
Monitoring	Symptoms Behaviors
Social Support	Maintenance Cultural

The Patient-Clinician Relationship

It may seem strange to include the clinician in a description of "self-management." It may also seem strange to use the term "patient" given that "self-management" implies that the "patient" is managing pain on his/her own and, therefore, not in a traditional "patient" role. As will be discussed, "self-management" can occur with just the efforts of the individual or can be "supported self-management" when it occurs in the context of professionally directed care.[12]

With the advent of sophisticated medical technologies and the increasing bureaucratization of medical care, communication between practitioners and patients has become increasingly hierarchical, administratively efficient, and impersonal. While such efficiencies can support the practice as a business, it tends to be woefully inadequate for addressing the needs of people with chronic pain.[13] A common complaint of both patients and clinicians is the lack of office time to address all the associated pain issues adequately.

Patients and their clinicians often bring two very different perspectives to the therapeutic relationship. Clinicians can offer a deep understanding of how pain develops, how best to treat it, and how and when to address concomitant comorbidities. In contrast, patients bring first-hand knowledge of what it is like to have the condition and how it affects daily life. Patients also know what seems to make sense to them and what they are willing to try. Integrating self-care into chronic pain care offers both the clinician and the patient a role to play if it is to be successful. Self-care is not simply shifting responsibility for pain treatment onto the patient. Instead, it capitalizes on a richer knowledge of the patient's circumstances that can influence pain and offers the benefits inherent in a clinician-patient dyad where treatment objectives are mutually identified.[14] It also acknowledges the chronicity of the pain where curative efforts need to be redirected toward promoting the wellbeing of the individual through continuous care and iterative adjustment to self-management strategies.[15] It is well-documented that patient-centered care that allows patients to take an active role in their care leads to better patient experiences and outcomes in the long term.[16,17]

The foundation of a good patient-clinician dyad is mutual respect and trust. By definition, chronic pain will be long term, and the dyad will need to work together to build a productive relationship over a lifetime, which will involve overcoming challenges and setbacks and the making of compromises when medical evidence and feasibility/desires conflict. Mutual respect and trust can facilitate *shared decision making,* which is needed for navigating the uncharted waters of the individuals' journey with chronic pain. The dyad is also supported by a shared knowledge of the mechanisms of chronic pain, a rationale for trying various treatments, and awareness of potential adverse responses. *Goals setting* and *action planning* within the dyad bolster the decision making process by making it objective and measurable. Without goals and action plans, it would be impossible to know whether the intended progress was being made or when additional fine-tuning was needed. Each dyadic function will be discussed further.

Shared decision making. The importance of therapeutic rapport is well-studied as a foundational element in behavioral change, adherence, and improved outcomes.[18] The traditional biomedical model emphasizes the clinician's role as a knowledgeable authority dictating the course of treatment to exact a cure for the presenting problem. The biomedical model can work well when a cure is likely, but it can be frustrating for both parties when cures are not the norm—such as with chronic pain.[19] In a patient-centric model, the clinician can still serve as a knowledgeable partner but more in the spirit of providing options, pros and cons of those options, and offering encouragement to the patient to identify what will work best at a particular point. Placing the clinician in this role better matches the evidence, which largely supports approaches requiring patient cooperation and involvement.[13,20] Unfortunately, most patients in primary care practices do not feel like an equal partner with decision making about their pain care.[21] Thus there is still work to translate the concept of "patient-centric care" into actual pain management practice.[22]

Pain neuroscience education. For the patient-clinician relationship to work well, both parties must share a common framework for understanding pain (i.e. pain, pain mechanisms, how those mechanisms are best treated, and why). Pain neuroscience, translated for a lay audience, offers the patient-clinician dyad a common language for discussing pain, a rationale for both pharmacologic and non-pharmacologic treatment options, and a foundation for generating personalized hypotheses about what would be effective. One study of online videos for pain neuroscience education suggested that pain neuroscience videos should contain seven key topics: [23] (1) the multiple sources that contribute to the pain experience, (2) the bioplastic nature of our nervous system and pain, (3) pain not being an accurate index of tissue status, (4) pain education as a form of treatment, (5) pain being created in and distributed from the brain, (6) pain's protective role, and (7) pathologic pain that can become overprotective and sensitized. Interestingly, most online videos claiming to provide pain education did not address any of the above topics, with only one addressing all topics (i.e. "Tame the Beast: It's Time to Rethink Persistent Pain"). The most commonly included topics were pain being created in and distributed from the brain and pain's protective role. The least frequently covered topics were bioplasticity and the overprotective/sensitization pathology of pain. Given the wide variance in quality of online educational materials, sharing educational resources between the dyad members can help ensure quality, create a shared understanding of pain, and helps reinforce the relationship between the two parties.

Goal setting. Goal setting might be considered the strategic part of the patient-clinician relationship.[24] Here, short and long term outcomes can be assessed and identified. Goal setting provides an opportunity to obtain three valuable tools for pain management: (1) a means of identifying relevant outcomes (e.g. personal goal attainment), (2) a means around which treatment can be tailored, and (3) a means of predicting the success of other treatments (e.g. a goal for increased step counts may predict improvements in pain interference).[25] Setting goals in the context of pain management adds structure to the management process and creates opportunities to evaluate progress. Goal setting refers to the choosing of goals and identifying the criteria by which a goal is evaluated. For example, if a patient sets a goal for pain reduction, it is important to identify how much pain reduction would constitute the achievement of that goal (e.g. complete remission?, 30%?). Setting goals that are reasonable and just slightly difficult to reach usually works best in pain management. Heapy et al. identified seven categories commonly associated with goal setting for pain self-management. These include goals for physical activity, functional status, wellness, recreational activities, house/yard work, socializing, and work/school activities.[26] Again, while an individual can set goals, including goal setting as part of the patient-clinician relationship offers an opportunity for the goal to be acknowledged publicly and allows the clinician to reinforce goal achievement.

Action planning. Whereas goal setting was the strategic component of pain self-management, action planning is the tactical component. By working on an action plan together, the dyad can identify specific behaviors that need to occur to turn goals into actions. Once actions are agreed upon, the patient then needs to act on the plan. This is known as "goal striving."[27] Depending upon the outcome of the actions, the clinician can then reinforce or assist in developing alternative plans. The clinician's involvement in action planning helps keep the clinician in touch with what the patient is attempting to accomplish and can serve as a reminder to ask about the entire treatment plan (i.e. both medications and self-management) on the next visit. Evidence suggests that when clinicians are active partners in encouraging and planning for self-management, patients learn more readily, manage symptoms and side effects better, and show better adherence to the overall treatment plan.[28]

Self-Efficacy Building. An objective of any self-management program is to have the individual with pain feel self-efficacious in performing the skills used to manage and control pain. The patient needs to go beyond simply learning about the skills to experiencing success through using the skills. This paves the way to self-efficacy, so he/she feels capable of managing pain in various situations in the future. Historically self-management skills have been taught in formal therapy supported by a therapist or coach. Once mastered, the individual would graduate therapy to become independent self-managers.

Nine non-pharmacologic therapies for chronic pain have sufficient evidence for broad implementation.[29] These can be grouped into three categories and include:

- psychologically based therapies (i.e. Cognitive-Behavior Therapy (CBT), Acceptance and Commitment Therapy (ACT), Mindfulness-based Stress Reduction (MBSR)),
- exercise and movement therapies (i.e. Exercise, Yoga, Tai Chi),
- manual therapies (i.e. manipulation, acupuncture, massage).

These therapies include skills that promote self-management to gain personal control over pain and symptoms, psychological flexibility to allow improved functioning in the context of pain, and empowerment to feel efficacious in managing pain between clinician visits or medication dosages.

The individual components of each of the above therapeutic options tend to overlap with one another and represent a set of skills to be learned, practiced, and mastered in support of better pain management more generally. Mastery of these *skills* can directly improve pain and functional status and provide an experientially based foundation for self-efficacy. Given that real-world applications of these skills can present challenges, training in *problem solving techniques* and methods of *personalizing* the skills to the unique circumstances of the individual can also help build self-efficacy to ensure long term success with pain self-management.

Skill building. There are many skills embedded in traditional therapies that can be learned and used on one's own. A sampling of some of these skills includes the following and can be grouped into those that are primarily intrapersonal in nature and more overtly observable and associated with one's lifestyle.

Intrapersonal Skills

- *Relaxation* – there are many methods of achieving mind and body relaxation (e.g. progressive muscle relaxation, visual imagery, meditation, biofeedback). All methods can work but require regular practice to establish a relaxation rhythm recognized by the body as a cue to relax.[30]
- *Sleep* – one night of poor sleep can interfere with coordination, mood, and mental agility for the next three days.[31] Behavioral sleep strategies and sleep hygiene skills can help individuals with pain get a better night's sleep despite the presence of pain.[32]
- *Mood management* – depression, anxiety, and anger are the big three emotions that can maintain pain and make it worse. These emotions need not be present at psychiatric levels to impact pain. Methods such as mindfulness meditation[33] and pleasant activity scheduling[34] can alter the background emotional milieu against which pain gets processed in the brain.
- *Stress management* – life can be stressful even without pain. When present, stress can make pain worse. Again, approaches such as pleasant activity scheduling[34] (e.g. engagement in daily brief, simple, pleasant activities such as going for a walk or spending time on a hobby) can help to reduce stress along with MBSR techniques.[35]
- *Reframing and cognitive restructuring* – when something is newly experienced, the mind creates a summary of that experience that is then recalled when interpreting the next encounter with a similar event. Using prior information in this manner facilitates faster mental processing and cognitive efficiency. While such efficiency can be helpful for day-to-day activities, this automatic thinking is problematic when it comes to chronic pain. Automatic catastrophic thinking, closed mindedness to potentially beneficial therapies, and low self-esteem are examples of unhelpful automatic thinking tied to pain. With chronic pain, automatic thinking can be challenged and altered to allow new possibilities for managing pain to emerge along with improved emotional responses to the reframed thinking.[36]
- *Resilience* – resilience refers to the personal strengths an individual can bring to bear on efforts to buffer the impact of pain. Such skills can be inherent or learned and include savoring each moment, finding gratitude, remembering positive events, conducting random acts of kindness, and learning one's signature strengths.[37]

Lifestyle Management

- *Exercise* – exercise benefits individuals whether or not they have pain and can include formal workouts, walking, water aerobics, or leveraging ongoing lifestyle activities.[38,39]
- *Pacing/graded activation* – activities can be paced either by time or broken into smaller tasks in a manner that reduces pain flare-ups, saves energy, and increases functioning and task completion.[40,41]
- *Diet and nutrition* – a healthy diet provides a solid foundation for wellness in general. Reduced weight can relieve burdened joints and make exercise more feasible. There is also some evidence that non-inflammatory diets, gluten-free, and hypocaloric diets can each have pain-reducing benefits.[42,43]
- *Acupressure* – acupuncture is an efficacious intervention for pain but requires a professional acupuncturist and, therefore, would not be considered a form of self-care. A personal version of acupuncture, acupressure, uses a similar philosophy but replaces the needles with the application of pressure (e.g. using the thumb, finger, or a blunt object). Evidence is emerging about the efficacy of this alternative approach for chronic pain self-management.[44,45]
- *Spirituality* – patient advocacy groups often mention the importance of spirituality in dealing with pain. Spirituality does not refer to any one theory or philosophy but references the importance of having a connection to something bigger than oneself and incorporates the formation of personal values and the search for meaning in life.

Problem solving. Individuals with pain face more challenges than people who are pain-free. Even minor tasks like carrying groceries up the stairs or driving to a relative's house for a visit can pose enormous feasibility challenges when in pain. There are structured problem solving processes that can be taught by a coach or adopted on one's own. Structured problem solving involves breaking a large problem down into smaller pieces to be addressed.[46,47] Structured problem solving comprises six steps. Step one involves identifying the problem. If there is more than one problem, then it needs to be broken into smaller pieces. Step two involves gathering information about the problem so it can be understood. Step three involves brainstorming a solution. For this step, all options can be on the table. Step four involves evaluating each of the brainstormed solutions in terms of whether the solution is (a) realistic and (b) favorable. Step five is the development of a work plan for addressing the problem. The work plan should include actionable items and the identification of potential barriers and means of addressing those barriers. Finally, Step six involves evaluating how the plan worked. If successful, congratulations. If unsuccessful, restart the process by revisiting Step one with a revised identification of the problem.

A common obstacle shared by many individuals with pain is how to incorporate the various pain management skills (reviewed above) into one's lifestyle. Many skills require consistent practice, the establishment of habit or a bodily rhythm, and the need to be integrated into an already crowded lifestyle. Knowing the skills but feeling blocked to implement them can have a deleterious effect on self-efficacy and ultimately the abandonment of self-management. While problem solving is not a pain management skill per se, it can help facilitate the mastery of the other pain management skills.

Tailoring and personalization. Similar to problem solving, tailoring and personalization involves molding generic pain management skills around the life of the individual with pain. Personalization can take many forms, such as selecting the elements of a skill found to be useful (e.g. using savoring resilience skills but not signature strengths). Skills can also be personalized in their timing/scheduling (e.g. using relaxation skills once a day for 20 min), modifying the skill to one's personal taste (e.g. using one's own music for relaxation rather than a scripted tape), or receiving personalized feedback on progress or barriers. Studies on the value of self-management personalization support the approach as a means of enhancing adherence and reinforcing one's self-efficacy for managing pain.[48]

Self-Monitoring

Monitoring how symptoms change over time and how specific behavioral changes can be more or less beneficial for a given symptom allows the individual to know what is working or what treatments can be stopped over the long term. Two types of self-monitoring will be described, monitoring for symptoms and monitoring behaviors.

Symptom monitoring. People have difficulty remembering how pain intensity fluctuates. If asked about pain intensity for the past week, people most likely recall the peak pain experienced for the week or report the pain intensity that occurred in the last several hours.[49–51] Being unable to objectively recount how pain was experienced over time makes treatment planning more difficult and makes it difficult to evaluate when and what treatments are working and which are not.

The most common symptoms monitored in the context of pain include pain intensity, the location of pain (using a body map), sleep problems, anxiety/depression, cognitive difficulties (e.g. memory and concentration), and fatigue. These symptoms represent a symptom cluster that commonly accompanies pain and other chronic diseases. This symptom cluster remembered by the acronym s.p.a.c.e. (sleep, pain, affect, cognition, energy) has been identified in both human and animal models as an index of "unwellness."[52] Monitoring s.p.a.c.e. over time can provide an ongoing account of how these symptoms interact, worsen, or improve compared to each other or with a given treatment.

Behavioral monitoring. Many of the self-management strategies require behavioral changes to be made. Thus monitoring or tracking the use of individual self-management skills can help with adherence and habit formation. For example, if an individual wishes to learn relaxation skills, it can be helpful to monitor time spent practicing relaxation daily. The same could be helpful if the individuals were trying to increase exercise time or monitor dietary intake. Behavioral monitoring helps establish routines but can also be used in combination with symptom monitoring to identify which behavioral changes are beneficial in altering the s.p.a.c.e symptom cluster.

Social Support

Good social support has been shown to buffer the impact of chronic pain on disability and reduce the amount of therapy needed.[53] This does not mean that people with pain need hundreds of friends; rather, just a few close acquaintances can be fine.[54] Although defined as a personal experience, people often need to share the experience of pain with others (i.e. to tell others about their journey with pain). Pain is often invisible, and therefore the only way to let others know what is being experienced is to verbally share it with others. Here we discuss two aspects of social support: relationship maintenance and cultural considerations.

Relationship maintenance. Pain is not experienced in a vacuum but rather in the context of relationships with others, such as family, friends, workplace employers/colleagues, and healthcare clinicians. Each of these relationships offers an opportunity for support both in physical terms (e.g. helping with tasks, offering physical assistance) or psychological (e.g. displaying empathy, offering encouragement, simply listening). Not all people know how to help someone with pain, nor do patients always know how best to ask for help. Communicating effectively with each social group is best done using assertive communication skills where each party gets heard, each has an opportunity to set priorities and limits, and compromise is always an option.[55]

Cultural considerations. Self-management must be considered through the lens of one's culture. Some components of self-management will work well in some cultures but not in others. For example, using assertive communication, taking time to meditate, engaging in water aerobics, or using acupressure could be viewed negatively or banned for some people in some cultures. Clinicians recommending self-management to their patients should be aware of such considerations and work with the patient (see "The Patient-Clinician Relationship" above) to set goals and develop action plans consistent with patients' culture. Self-management that includes a consideration of culture can positively affect outcomes and adherence.[56]

Evidence Supporting Pain SMPs

The United States Veterans' Administration has placed education and pain self-management as Step 1 of their "Stepped Care Model for Pain Management."[57] In this model, self-management functions as both a preventive strategy for general wellness and as a first line approach for persistent pain. If insufficient relief results, then progressively more intensive approaches can be tried in primary care (i.e. Step 2 - medications, psychological therapies). Step 3 involves secondary consultation (e.g. rehabilitative medicine, multi-disciplinary pain medicine teams, mental health/substance use interventions), and finally, Step 4, tertiary pain centers, includes interventional pain medicine or multi-disciplinary pain programs. A similar model was developed in the United Kingdom by the British Pain Society known as the Pain Care Pathway, which begins with diagnostics and treatment planning, including education and self-management before progressing to more intensive or invasive options.[58,59]

Finding the Relevant Comparator

Before one can decide whether pain SMPs are efficacious, it is important to ask the question, "efficacious for what?" Is the objective of pain SMPs to cure pain? No. Is the objective of pain SMPs to have superior outcomes to or replace interventional medicine? No. Is the objective to outperform or replace traditional therapies, such as medications, physical therapy, or CBT? Again, no. To understand the proper comparator for pain self-management, remember the intended purpose of self-management within the overall continuum of pain treatment options. If following a stepped care model (as mentioned above), the real-world comparator for pain self-management would be nothing given it is supposed to be offered prior to other treatments requiring therapists or treatments that do not actively involve patients. Perhaps the most informative clinical studies of pain self-management would be those that evaluate the optimal placement of self-management in the continuum of care and the characteristics of individuals most likely to benefit from that placement.

However, most of the evidence base supporting self-management consists of "horse races" between self-management and treatment as usual (TAU) or active interventions. All of these are comparators that occur at Step 2 or beyond in the model. For example, TAU often involves a wide array of medications and other active interventions from multimodal professional care (e.g. PT, CBT). Thus the published studies on self-management programs may actually underestimate the true effects given the comparators included treatments further up the stepped care hierarchy and likely selected patients with more refractory pain than would be expected to have benefited from the first step of a real-world stepped care model.

Review of the Evidence

A systematic review and meta-analysis of SMPs for low back pain examined 13 randomized control trials (RCTs).[60] In this study, pain SMPs were found to convey moderate effects for reducing pain intensity over one year. Similarly, moderate effects were shown for disability up to three months and then smaller effects at six months to one year. Of note, none of the 13 RCTs (combined n = 2188) reported any serious adverse events being associated with SMPs, suggesting its relative safety compared with other forms of pain treatment.

To benefit from self-management, participants need to actually participate and use the skills. In one study conducted in the UK, the retention rate for SMP was quite favorable, with the uptake of the program being 71% (n = 376). Following the seven week course, they still reported an 82% completion rate. Six months after precourse assessment, participants reported significantly improved activation, health status, depression and anxiety, decreased pain intensity and interference, and improved self-management skills.[61] A unique feature of this SMP that likely contributed to the retention and positive outcomes was that it was co-led by a physician and patient dyad.

Despite the study above, concerns over dropouts may be more the norm, especially in rural primary care populations. In one such study using bivariate analyses, early dropout was associated with being male, being younger, having a history of substance abuse, having a trauma history, receiving unemployment/disability benefits, being of low literacy, having higher catastrophizing scores, having higher daily opioid use, and holding a narrow biomedical understanding of pain. Logistic regression analyses revealed a reduced set of concerns, with the strongest predictors of dropout being a history of substance abuse, trauma, catastrophizing, and holding a biomedical understanding of pain.[62]

Overall, there appears to be support for the inclusion of self-management as an initial intervention for most forms of chronic pain. While it will not be sufficient for all individuals, it does appear to provide a good foundation for gaining some relief and improved function as an adjunct to traditional care. There also appears to be very little difference in effectiveness between the different forms of self-management, i.e. whether it is professionally delivered versus lay led, or whether it is individually administered or in group settings.[63]

Pain Self-Management in the Context of Primary Care

Chronic pain is the most common reason for seeking health care, and most cases are initially seen in a primary care context.[64] Unfortunately, these clinicians may not be the best equipped to manage such a complex condition. Eighty percent of American medical schools have no formal pain education in their curriculum, and those that do, report five or fewer hours of mostly basic science education related to pain.[65] Many residency programs similarly miss the mark by continuing to emphasize an outdated biomedical model of care focused on interventions for "curing" pain rather than multi-disciplinary management.[13] It is well known that the traditional model often fails to provide adequate relief for most, has a high rate of adverse events, and in the case of the more invasive approaches, lacks sufficient evidence to support their use.[66–68]

Self-management can offer primary care clinicians a means by which to diminish the pain experience and increase function with little cost and few adverse events. Unfortunately, the uptake of self-management in primary care practices has been slow and may require a cultural shift where the acceptance of pain as a biopsychosocial and perceptual experience requiring individualized and targeted care [69] is adopted by a host of stakeholders including patients, clinicians, payors, and healthcare systems.[70,71]

Reengineering the Point-of-Care

Better integration of SMPs into primary care may require the point-of-care to be slightly reconfigured.[72] From the clinician's perspective, high-quality primary care pain management programs need these six elements.[28]

Local linkages between the Primary Care Clinician (PCP) and community self-management resources (e.g. exercise classes, pools, yoga).
The PCP requires healthcare organizations that place value on multi-disciplinary pain care.
The PCP needs to truly place value on self-management and appreciate the benefits of patient empowerment in successful pain care, both in terms of patient outcomes and economic benefit.
The PCP needs a structure for delivering self-management that includes roles and tasks of team members for educating patients, assessing needs, setting goals, and developing action plans.
The PCP needs administrative support for incorporating evidenced pain care into daily practice.
The PCP needs clinical informatics systems that remind clinicians of self-management resources and skills being used by patients and their individual outcomes.
A second qualitative study captured the patients' perceptions and those of the clinician about barriers associated with patients' ability to engage with pain self-management. These barriers included:[73]
Patients felt that clinicians waited too long to recommend or offer advice on self-management strategies.
Patients felt that clinicians were rushed and failed to listen carefully to their concerns.
Patients felt that clinicians offered only generic self-management information, if any at all.
Patients felt that they were on their own to learn about self-management and felt unsupported in this aspect of pain care.
Clinicians felt conflicted about offering self-management when they still believed in the biomedical model and the possibility of "curing" chronic pain.
Clinicians felt conflicted about offering self-management advice when they were not familiar with the quality of the information.
Clinicians found it challenging to discuss the biopsychosocial model of care and felt that many patients would not be ready or willing to participate.
Both clinicians and patients agreed there was an over-emphasis on medications for pain and a need for greater acceptance of alternatives.
Both clinicians and patients agreed that for self-management to work, there also needed to be greater continuity of care where self-management was genuinely incorporated into the flow of primary care practice.

From what has been discussed, many of these barriers can be overcome by properly placing self-management at the front-end of a practice's approach to pain care. There is also an apparent mismatch between clinicians' comfort level in recommending self-management and the patient's desire for such approaches to be used between office visits and a primary care practice.

Explaining Self-management to Patients

Another ongoing challenge for primary care clinicians has been broaching pain self-management with patients. There is fear that the concept of self-management will be rejected, the recommendation will damage the relationship, or PCPs may not feel comfortable explaining why self-management is real pain treatment.[74] Over the past three years, faculty within the Chronic Pain and Fatigue Research Center at the University of Michigan have participated in a statewide initiative to educate primary care physicians about optimal pain management, including the use of self-management. The following is an example of how the rationale for self-management can be presented to patients.[75]

How to ERASE SPACE

When pain is chronic, there is rarely a problem in a specific set of damaged tissues where the pain seems to be felt (e.g. in the leg or back). Instead, chronic pain is considered to result from how pain is "processed" within the brain.[76] Unlike acute pain, chronic pain is often accompanied by the s.p.a.c.e. symptom cluster (described above), which includes problems with sleep, pain, affect, cognition, and energy. Pain processing involves mechanisms that also contribute to these other symptoms; thus pain and these other symptoms tend to show up together. Neurobiologically, pain and these other symptoms share the same neurotransmitter system in the brain (e.g. glutamate, GABA, norepinephrine, serotonin) and overlapping cortical representation (e.g. amygdala, insula, prefrontal cortex, hippocampus, anterior cingulate).[77] Given this shared neurophysiology, patients with chronic pain tend to present at the clinic with a complex list of problems. However, these problems tend to all come from the same source, which accounts for this complexity.[78] Shared neurophysiology offers opportunities for better pain treatment. While our pain drugs may offer only modest relief for pain, we do have relatively good treatments for sleep, mood, and fatigue. Targeting these other symptoms can have indirect benefits on pain (e.g. addressing poor sleep can also be beneficial in reducing pain).[52]

Many of the self-management skills used for pain (described above) are generic illness management strategies and can thus benefit each symptom within the s.p.a.c.e. symptom cluster. For example, exercise has demonstrated benefits not only for pain but also sleep,[79] mood,[80] fatigue,[81] and cognitive functioning.[82] The various self-management approaches can be grouped into categories addressing emotions (e.g. pleasant activity scheduling, stress management), reflections (e.g. reframing, relaxation), actions (e.g. exercise, pacing), sleep (e.g. behavioral and sleep hygiene), and environmental factors (e.g. social support, communication). The self-management categories can be remembered by the acronym ERASE. Thus when clinicians are addressing the rationale for using self-management for pain, the goal for patients is to use self-management approaches to ERASE the SPACE symptom cluster (Table 62.2).

Reimbursement

Perhaps the biggest barrier to integrating self-management into routine pain care is the issue of reimbursement. Historically, resistance to self-care was generated from the misconception that psychosocial constructs were of lesser importance than "real biologic" causes of pain and might connote patient fabrication of concerns. Self-management was also perceived as inefficient given the need for clinician involvement in shared decision making, goal setting, action planning, and monitoring (see above). To proponents of the biomedical model, where psychosocial factors represent non-essential add-ons, such opposition is understandable. However, the lack of benefit often associated with the biomedical model supports a need to reconsider how best to utilize clinicians' time. Neuroscience supports the notion that chronic pain is a perceptual problem rather than tangible damage of peripheral tissues. Clinicians are realizing the need to treat the perception of pain

TABLE 62.2 ERASE SPACE

Self-Management Categories	CHRONIC PAIN SYMPTOM CLUSTER (s.p.a.c.e.)				
	Sleep Problems	Pain Intensity and Distribution	Affect: Depression Anxiety	Cognition: Memory Concentration	Energy: Fatigue
Emotions	Examples: Pleasant activity scheduling, stress management, journaling				
Reflections	Examples: Relaxation, mindfulness, reframing				
Actions	Examples: Exercise, pacing, diet/nutrition, acupressure				
Sleep	Examples: Behavioral sleep strategies, sleep hygiene				
Environment	Examples: Social support, ergonomics, assertive communication skills				

and how it is processed rather than focusing on trying to fix broken body parts that might be associated with pain.

Recently, payors discovered that more diagnostics and more procedures were not producing better outcomes, and as a result, priorities are beginning to shift away from curing chronic pain to its management.[13,14] When patients are encouraged to understand self-management in the context of ongoing care, clinicians work in a synchronized collaborative manner to tailor treatment to the individual patient, and reliance on specialists is reduced, and outcomes improve.[83] Focusing on self-management extends clinicians' reach rather than simply usurping precious clinical encounter time. In doing so, patients are empowered to productively communicate with clinicians about treatment preferences and utilization of self-management strategies and assess the benefits of these strategies before progressing to other more costly or invasive treatments.[16,84–86] Recently, the United States Department of Health and Human Services report on Pain Management Best Practices included recommendations for broader reimbursement for non-pharmacologic therapies, including self-management approaches.[87]

Even when a practice completely adopts the rationale for self-management, finding the time and staff to properly administer SMPs in the office environment remains problematic. The education, goal setting, and action planning activities all take time that does not fit neatly into the 15 min office visit. Utilizing other team members (e.g. nurses, physical therapists, occupational therapists) to deliver face-to-face coaching can be effective,[88–94] but still may not be a feasible option in many practices. Digital pain self-management is gaining popularity and can help primary care practices expand their reach between office visits. These digital programs (also called e-Health or mHealth) can involve interactive voice responses, telephonic coaching, website-based self-management, and smartphone app-based approaches.

Digital SMPs

Digital SMPs are usually offered in either guided (with a therapist/coach) or unguided (self-directed) formats. Unguided formats can either be static content only sites or semi-automated ones assisted by logic-driven personalized messaging.

Only a handful of studies have been able to directly compare the benefits of guided versus unguided approaches. However, a meta-analytic study suggested that the guided interventions work best when a human coach can help with motivation, clarification of difficult concepts, personalization, and adherence.[95] At least one digital intervention, using a version of ACT (i.e. ACTonPain), explored this question in a three arm RCT (i.e. guided vs. un-guided, vs. usual care). The guided version revealed the best outcomes overall but at a significantly greater cost. A health economics analysis of this study suggested that depending upon a society's willingness to pay, the unguided version may be preferable, given it still produced significantly better outcomes than the usual care group but at much reduced cost.[96]

Digital Pain Self-Management: Pros and Cons

With digital self-management for pain, it can be a bit like the "Wild West." There are over 900 digital products targeting pain management,[10] with the majority of those being developed without the guidance of a pain expert.[97] There have been some attempts to evaluate the health information quality of websites using either the JAMA score criteria or the HONcode system. One study using these methods to evaluate websites about fibromyalgia found that overall, the quality of health information on most websites was rated as poor and difficult to understand.[98] Not-for-profit organizations tended to have the best information. An additional concern about most online self-management resources is that the majority of sites have been made available to the public without ever being tested for efficacy.[10,97,99]

Given the variability in quality, it is not surprising that many clinicians have been hesitant to refer their patients to digital self-management resources. One study found that only half of the healthcare clinicians surveyed would recommend online self-management to their pain patients.[100] The reasons for not using this resource included a lack of confidence in self-management generally and lack of knowledge about the quality and availability of existing resources.

From the patient perspective, ideal digital SMPs should offer information and knowledge about pain and its treatment, methods for obtaining balance between managing pain and normal life activities, and a means of communicating and engaging with others and receiving social support.[101] digital self-management resources are far from this ideal. A review of current smartphone apps for pain management found that most included only 4/14 potential techniques with some of the more comprehensive programs offering 8/14.[10] The most frequently offered technique was meditation and guided relaxation, followed by the ability to monitor symptoms and self-tailoring strategies. Only a few apps offered features supporting social support or clinician communication, and none offered the ability to tailor for cultural needs. Digital

self-management apps offer some but not most of the components typically found in traditional face-to-face versions of SMPs. Clinicians may want to augment their practices with these resources but will need to carefully vet the scope and quality of the digital resources they are offering their patients.

Within the cornucopia of digital products, there are a few that have been developed by experts and evaluated in RCTs. These studies generally support digital benefits being similar to those seen with traditional in-person self-management. A systematic review of unguided digital SMPs demonstrated significant short- and long term improvements in pain intensity and depression and short term improvements on catastrophizing and self-efficacy.[102] The review concluded with the recommendation to increase the availability of efficacious digital self-management options for routine care.

Future Directions

Self-management appears to be best positioned at the front-end of pain care in either face-to-face or digital formats and as either guided or unguided experiences. Cost savings appear possible when delivered in an unguided digital format without compromise to outcomes for many individuals. Self-management, however, is best used in the context of an overall model of care that can be scaled up in intensity or back depending upon need. Self-management is not likely to be sufficient for most as monotherapy but can be used as an extension of care between office visits.

Perhaps one of the trickiest problems with self-management remains the issue of engagement. Engagement can be conceptualized as coming in two forms: simple engagement versus "effective engagement."[103] If using a self-management website, an individual might log in just to browse. This would be simple engagement (i.e. the individual is present). However, they may not be actively engaged with the self-management skills offered on the site. The person would need to spend time on the site, learning and applying the skills for self-management. This distinction between simple and effective engagement might account for the often unintuitive association between website usage and outcomes [104,105] (e.g. little engagement can be associated with good outcomes and high engagement with poor outcomes). Outcomes are not likely to change simply by having sustained engagement without effective involvement. In order to enhance effective engagement, future digital SMPs will need to utilize a "person-based" approach to development that considers users' knowledge, skills, behaviors, motivation, culture, and context for using the program. There are opportunity costs of using the digital product rather than engaging in other activities. The costs and benefits need to favor the digital product if effective engagement is to occur. Effective engagement is also more likely if the content is matched to the educational level or literacy of the participant. Tailored messaging that utilizes knowledge about the participant's context or situation can enhance motivation for effective engagement. Unguided self-management can be effective, but the effect sizes are smaller than when a coach is used. Coaches add an element of supportive accountability and the sense that the participant is not having to deal with pain completely on their own. Finally, effective engagement can be enhanced simply by having a trusted clinician recommend its use. While many digital resources are freely available, a recommendation from a trusted healthcare clinician is likely to increase engagement with the resource.[103]

As alternatives to opioids continue to be required and a desire to incorporate a more person-centric multi-faceted approach to pain management persists, self-management will remain an important element of care. Improved clinician and payor education could increase the perceived value of the approach. Improved reimbursement will similarly contribute to broader acceptance of the approach. Finally, investment in informatics infrastructures to support the delivery, tracking, and sustainability of self-management over time has been a key missing element that could facilitate more wide scale deployment and adoption of pain self-management.

Key Points

- Pain self-management is best placed at the initiation of a comprehensive pain management program.
- Self-management is what patients use to manage pain between office visits to healthcare clinicians and more traditional care.
- Self-management does not replace or compete with traditional forms of pain treatment.
- Self-management needs to be better incorporated into routine pain care.
- The traditional primary care practice may need to be redesigned to make optimal use of pain self-management by adding informatics for monitoring progress and staff who can support patients when needed.
- Digital resources can augment self-management, but the quality of sites and apps varies greatly and needs to be vetted.
- Guided /coached self-management is slightly more efficacious than unguided resources, but patients can still benefit from the latter at a lower cost.
- Clinicians need to ask patients about their use of self-management with the same enthusiasm as medications and other more traditional forms of pain care.

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PART 6

Neural Block and Interventional Techniques

63

Neurolytic Agents, Neuraxial Neurolysis, and Neurolysis of Sympathetic Axis for Cancer Pain

HEATHER A. COLUMBANO, AMIT GULATI, ROBERT W. HURLEY

Neurolytic therapy, for the appropriate patient, may result in significant improvement of quality of life and possibly improved function. Few other interventional pain therapies have such extreme risk/benefit profiles requiring targeted patient selection and meticulous procedural technique. Evaluating neurolysis as a therapeutic option is usually reserved for end-stage therapy, primarily for patients with refractory cancer pain resulting from the possibility of severe side effects. For instance, neuraxial neurolysis can provide profound pain relief for patients with pain related to invasive tumors involving the pelvis, but this approach often also leads to loss of bowel or bladder function and may well also produce weakness in the lower extremities. It should also be emphasized that relief from neurolytic blocks is usually not complete, as most patients with cancer pain have multiple sources of their pain. Neuraxial neurolysis is an important treatment modality for patients *in extremis*. Neurolytic agents available in the United States for common use in the neuraxis include ethanol and phenol. The five criteria for neurolysis[1] are (1) the presence of severe pain, (2) the failure of less invasive techniques to relieve the pain, (3) the presence of well localized pain, (4) the relief of pain with diagnostic local anesthetic blocks, and (5) the absence of undesirable effects after diagnostic blocks (Box 63.1).

Neurolytic blocks can be peripheral, neuraxial, or visceral. Of the three, visceral blocks are most commonly performed. In the case of peripheral neurolytic nerve blocks, blocking mixed motor and sensory nerves can cause motor deficits leading to loss of functionality for the patient. In addition, peripheral neuritis and deafferentation pain are potential painful consequences, whereas the block itself is not predictably permanent.[1] Finally, the patient may also be dissatisfied with the subsequent numbness of the area and complain of symptoms of *anesthesia dolorosa*. Neuraxial neurolytic blocks, including intrathecal and epidural alcohol or phenol neurolytic blocks, are rarely used today because neuraxial analgesics including opioids, local anesthetics, and clonidine can effectively and safely be used to treat cancer pain. Where an intrathecal drug delivery system can provide widespread pain relief that can be adjusted to accommodate many scenarios, a successful neurolytic block may have to be repeated with changes in the pathologic condition, such as the presence of new metastatic lesions. In such cases, it is impractical to perform subsequent subarachnoid neurolytic injections because of their attendant risks, whereas an indwelling intrathecal (and occasionally epidural) drug delivery system will cover new areas of pain and continue to be useful. In contrast, neurolytic blocks have a less financial burden than implantation of intrathecal drug delivery systems.

• Box 63.1 Criteria for the Use of Neurolytic Blockade

- Pain is severe and unremitting
- Pain is unresponsive to medical management
- Pain is relieved with diagnostic blocks using local anesthetic
- No undesirable effects appear during local anesthetic blocks
- Pain is well localized
- Pain affects the patient's function
- Patient is not a candidate for neuraxial medication delivery systems
- Patient has failed neuraxial medication delivery
- The patient can perform informed consent or has appropriate advance directive

While neurolytic blocks are effective in treating visceral pain syndromes, there may be less efficacy or shorter duration of effect when treating somatic pain syndromes or lymphatic pain syndromes. Stretching, compressing, invading, or distending visceral structures can result in poorly localized, noxious visceral pain. Patients experiencing visceral pain often describe the pain as vague, deep, squeezing, crampy, or colicky. Other signs and symptoms include referred pain (e.g. shoulder pain that appears when the diaphragm is invaded by a tumor) and nausea and vomiting because of vagal irritation.

Visceral pain associated with cancer may be relieved by oral pharmacologic therapy, which classically includes combinations of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and co-adjuvant therapy (i.e. anti-convulsants and tricylic antidepressants). NSAIDs have fallen out of favor with some clinicians for the treatment of chronic pain because they have been implicated in thrombotic events. Besides pharmacologic therapy, neurolytic blocks of the sympathetic axis are also effective in controlling visceral cancer pain and should be considered as important adjuncts to pharmacologic therapy for the relief of severe visceral pain. These blocks rarely eliminate cancer pain because patients frequently experience somatic and neuropathic pain. Therefore oral pharmacologic therapy must

be continued in the majority of patients with advanced stages of their disease. The goals of performing a neurolytic block of the sympathetic axis are to maximize the analgesic effects of opioid or nonopioid analgesics and reduce the dosage of these agents to alleviate side effects. This chapter reviews the technical approaches and pharmacologic agents used for neurolytic blocks, neuraxial neurolysis, and neurolysis of the sympathetic axis for cancer pain.

Neurolytic Agents (Table 63.1)

Alcohol

Ethyl alcohol (ethanol) is the classic neurolytic agent first reported by Dogliotti in 1931 for intrathecal injection.[2] Anhydrous ethanol is commercially available undiluted (approximately 100% concentration) but will absorb a small amount of water from the air upon exposure to the atmosphere. Although neurolytic blocks have been shown to require a concentration of 33% or greater to effect neurolysis,[3] the most common concentrations used are ≥80% when diluted with contrast medium or local anesthetic. The neurolytic action of alcohol is produced by the extraction of neural cholesterol, phospholipids, and cerebrosides, and the precipitation of mucopeptides.[4] These actions result in sclerosis of the nerve fibers and myelin sheath, leading to demyelination.[5] The basal lamina of the Schwann cell sheath remains intact, allowing for new Schwann cell growth, thereby providing the framework for subsequent nerve fiber growth. This framework encourages the regeneration of axons, but only if the cell bodies of these nerves are not completely destroyed.[6] The pathway of degeneration is nonselective and can be observed in peripheral nerves and spinal nerve roots following intrathecal injection. Areas of demyelination can be seen in posterior columns, Lissauer's tract, and the dorsal root, followed by Wallerian degeneration to the dorsal horn.[7] Intrathecal alcohol injection results in rapid uptake of alcohol and variable injury to the surface of the spinal cord.

Ethanol is quickly absorbed from the cerebrospinal fluid (CSF) so that only 10% of the initial dose remains in the CSF after 10 min and only 4% after 30 min.[8] The rapid spread from the injection site means larger volumes are required than for phenol, which in turn may result in local tissue damage.[9] In the case of celiac plexus blocks, alcohol is rapidly absorbed into the bloodstream. It has been shown that serum ethanol levels up to 54 mg/dL can occur after a celiac plexus block.[10] However, following the intrathecal administration of alcohol, it is unlikely there will be significant vascular uptake. Ethanol has a specific gravity of less than 0.8, and CSF has a specific gravity of slightly greater than one. Within the CSF, alcohol is hypobaric and will move against gravity, "floating" upward. Therefore positioning of the patient is an extremely important factor to consider when planning the procedure.

The use of ethanol as a neurolytic agent has been associated with a disulfiram-like effect, acetaldehyde syndrome. Case reports include patients taking moxalactam, a β-lactam antibiotic that inhibits aldehyde dehydrogenase, documented disulfiram-like effects, and another taking 1-hexyl carbamoyl-5-fluorouracil, an anticancer drug, experienced similar symptoms.[11] The patients experienced flushing, hypotension, tachycardia, and diaphoresis within 15 min of alcohol administration. The symptoms resolved 4–6 h later, and efforts were undertaken to stabilize hemodynamics. Both cases occurred after celiac plexus blocks. The pain practitioner needs to recognize medications that may cause disulfiram-like effects, such as chloramphenicol, β-lactams, metronidazole, tolbutamide, chlorpropamide, and disulfiram, after peripheral neurolytic blocks with alcohol.[12]

Perineural administration of ethanol is associated with burning dysesthesias in the distribution of the nerve. This sensation is often extremely unpleasant for the patient and can last from a few minutes to a few weeks. To alleviate this outcome, local anesthetic is administered prior to the use of ethyl alcohol. The use of this initial dose of local anesthetic can also provide diagnostic guidance on the correct location for the neurolytic that has enormous importance. The administration of ethanol for the purpose of neurolysis can have catastrophic consequences. It has been associated with both transient and permanent paraplegia in both celiac plexus and intrathecal blocks. It has been postulated that these effects are secondary to vasospasm of the spinal arteries by the direct action of alcohol or direct damage to the spinal motor nerves.[9]

TABLE 63.1 Characteristics of Chemical Neurolytic Agents

	Alcohol	Phenol
Physical properties	Low water solubility	Absorbs water on air exposure
Stability at room temperature	Unstable	Stable
Concentration	100%	4%–8%
Diluent	None	Glycerin
Relative to CSF	Hypobaric	Hyperbaric
Injection sensation	Burning pain	Painless, warm feeling
Onset of neurolysis	Immediate	Delayed (15 min)
CSF uptake ends	30 min	15 min
Full effect of neurolysis	Three to five days	One day

CSF, Cerebrospinal fluid.

Phenol

Phenol has a benzene ring with one hydroxyl group substituted for a hydrogen atom. It is usually prepared by the hospital pharmacy because it is not commercially available in premixed liquid form. Phenol is poorly soluble in water and, at room temperature, forms only a 6.7% aqueous solution. It has a shelf life of approximately one year if refrigerated and shielded from light exposure. When phenol is exposed to room air, it oxidizes and turns a reddish color. Phenol is frequently prepared with sterile water, sterile saline, or glycerin. When prepared with glycerin, it has limited anatomic spread, and, hence, injections are well localized. In rats, the aqueous solution of phenol has a greater ability to penetrate the perineurium and produce greater endoneurial damage than glycerin preparations, but there is no difference in the results following intraneural injection.[13] Unlike alcohol, phenol injection has an initial local anesthetic effect. It is not associated with localized burning but instead creates a sensation of warmth for a short time after injection. The distribution of this sensation can help the practitioner verify proper needle placement similar to a diagnostic local anesthetic injection. Concentrations of 4%–10% are typically used for neurolysis. When phenol is prepared in glycerin, it has a specific gravity of

1.25, making it hyperbaric. Preparations of phenol in glycerin are highly viscous, which may make administration through a small (22- or 25-gauge) spinal needle difficult.

Putnam and Hampton first used phenol as a neurolytic agent in 1936. Mandl used it for a sympathetic ganglion block in animals in 1947.[14] Phenol was first used as a medication in an intrathecal injection in humans in 1955.[15] It was once believed that phenol's neurolytic effects might be because of local ischemia because of its greater affinity for vascular tissue than neural tissue.[16,17] Racz found that, unlike epidural injection, tissue destruction resulted after intrathecal injection even though the vasculature was intact in the areas of spinal cord destruction.[18] This finding points toward direct neurotoxic effects rather than effects secondary to local ischemia. Phenol's effects may be a combination of direct neurotoxic and ischemic effects.[19] Originally, it was surmised that phenol had a selective effect on small-diameter, unmyelinated nerve fibers, such as c-fiber afferents and lightly myelinated A-δ afferents. Subsequent studies have shown that phenol concentrations determine the type and extent of nerve disruption. Dilute intrathecal phenol can produce a transient local anesthetic blockade, whereas increased concentrations can produce significant neural damage.[20] At concentrations <5%, phenol results in protein denaturation of axons and surrounding blood vessels. At concentrations >5%, phenol can produce protein coagulation and nonselective segmental demyelination.[9] Nathan confirmed the nonselective effects of phenol using histologic studies combined with evidence of electrophysiologic changes to Aα and Aβ fibers.[21] Smith showed that intrathecal phenol injections in cats and humans primarily destroyed axons in dorsal rootlets and the dorsal columns of the spinal cord. It was also noted to exert some effects on the ventral root axons.[22] Maher and Mehta noted that motor blocks by phenol were possible at concentrations greater than 5%, whereas intrathecal injections of less than 5% produced mostly sensory blocks.[23] At higher concentrations, the extent of damage can increase significantly, with the potential of axonal nerve root damage and spinal cord infarcts. Injections of high concentration phenol have also been associated with arachnoiditis and meningitis.[24]

Systemic doses of phenol over 8.5% are associated with toxic side effects. These effects initially are convulsions, followed by central nervous system depression, and, finally, cardiovascular collapse. Chronic long-term exposure may be associated with renal toxicity, skin lesions, and gastrointestinal effects. However, phenol is not classically used in long-term settings, and the customary doses of less than 100 mg are unlikely to produce any systemic effects.[5]

Compared to alcohol, phenol seems to facilitate axonal regeneration in a shorter period. Electrophysiologic studies comparing peripheral nerve destruction in cats showed that those injected with phenol had returned to normal by two months, whereas at the end of the same period, those injected with alcohol still demonstrated depression of compound action potentials.[25]

Glycerol

Glycerol is a colorless, odorless, viscous, liquid, polyol compound. It has three hydroxyl groups that result in high water solubility, and it is hygroscopic in nature. The glycerol backbone is central to all lipids known as triglycerides. When placed on nervous tissue, myelin disintegration and axonolysis occur in both myelinated and unmyelinated fibers. In the uninjured nerve, the c-fiber and lightly myelinated fibers are the most sensitive to neurolysis, requiring higher concentrations to destroy the heavily myelinated fibers. However, this order is altered in the injured nerve; the heavily myelinated fibers become very sensitive to the neurolytic properties of glycerol. In 1981 Hakanson was the first to use glycerol for neurolysis of the trigeminal ganglion.[26] The success is most likely related to a combination of the viscous nature of glycerol and resultant lack of spread into other sensitive structures, the low concentration required to destroy the abnormally firing myelinated fibers while preserving the uninjured sensory afferents. The use of glycerol for neurolysis is now primarily restricted to the neurolysis of the Gasserian ganglion.

Neurolytic Blocks

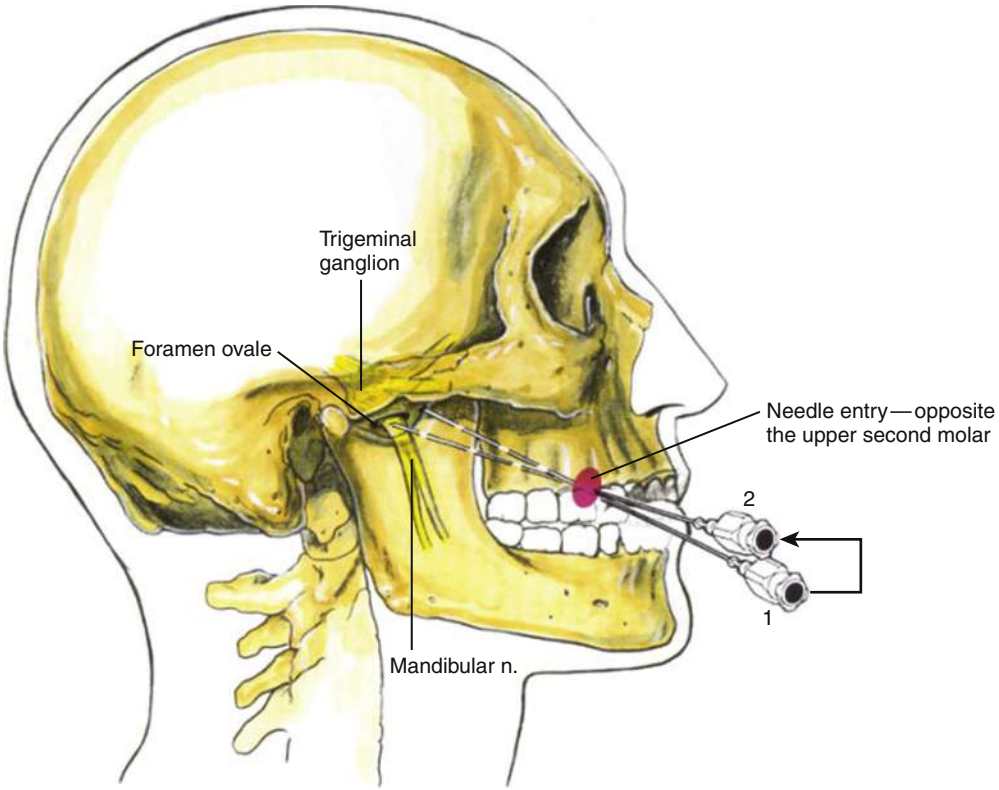
Neurolytic agents can be injected surrounding the peripheral nerves, along the neuraxis within the intrathecal or epidural spaces, or adjacent to visceral sympathetic nerves. Each of these sites of injection is associated with specific benefits, risks, and complications. Peripheral neurolysis can include injection into the trigeminal ganglion, truncal, upper, and lower extremities.[1]

Head and Neck

Gasserian Ganglion Neurolysis

Peripheral nerves in the head and neck are destroyed for a variety of reasons. These include blockade of the trigeminal ganglion for trigeminal neuralgia that is not responsive to medical management and for relief of cancer pain secondary to invasive tumors of the orbit, maxillary sinus, and mandible, and blockade of individual peripheral nerves in the head.

The Gasserian ganglion is formed from two trigeminal roots that exit the ventral surface of the brainstem at the midpontine level.[27] The roots pass forward and in a lateral direction, in the posterior fossa of the cranium, across the border of the petrous temporal bone. It then enters the Meckel's cave in the middle cranial fossa. The Gasserian ganglion contains the ophthalmic, maxillary, and mandibular divisions. A smaller motor root joins the mandibular division as it exits the foramen ovale. It should be noted that a dural pouch, the trigeminal cistern, lies behind the trigeminal ganglion. In Gasserian ganglion block, the needle is inserted approximately 2.5 cm lateral to the side of the mouth and advanced, perpendicular to the middle of the eye (with the eye in the mid-position) in a cephalad direction toward the auditory meatus.[28] When contact is made with the base of the skull, the needle is withdrawn and "walked" posteriorly toward the foramen ovale (Fig. 63.1). A free flow of CSF is usually noted, and fluoroscopy is then used to confirm the correct needle placement. Very small amounts (i.e. 0.1 mL increments) of local anesthetic or neurolytic agent (commonly glycerol) are injected to a total of 0.4–0.5 mL. Because of their different baricity, the patient remains supine if alcohol is used but placed in a sitting position with the chin on the chest prior to the injection of phenol. This maneuver localizes the phenol around the maxillary and mandibular divisions of the trigeminal nerve, avoiding the ophthalmic division and the risk of keratitis from loss of the conjunctival reflex. If glycerol is used, the patient is kept in a "seated"/head-up position. The pterygopalatine space is highly vascular, and significant hematoma of the face and subscleral hematoma of the eye can occur. Veins in the subtemporal region can be punctured, causing hemorrhage in the temporal fossa. Local anesthetic injection can lead to spinal anesthesia because the ganglion lies within the cerebrospinal fluid. Blockade of the motor fibers of the trigeminal nerve can interfere with mastication.[29] Oculomotor palsy, which results in



• **Figure 63.1** Trigeminal ganglion block: anatomy and technique. (Reprinted with permission from Brown D. *Atlas of Regional Anesthesia*. 3rd ed. Philadelphia: Saunders, an imprint of Elsevier; 2006: Figure 20-5.)

diplopia and strabismus, is usually temporary. Abducens palsy is also temporary, although cases of permanent lateral rectus palsy have been reported.[30] Spread of the neurolytic agent into the facial nerve results in paralysis of the facial muscles and inability of the eyelid to close, resulting in keratitis or corneal ulceration. Blockade of the greater superficial petrosal nerve may result in a lack of tear formation and conjunctivitis. Blockade of the acoustic nerve may result in deafness or dizziness. The delayed effects of Gasserian ganglion neurolytic block include trophic problems such as keratitis, ulcerations in the nose, and erosions in the mouth. These disturbances usually occur after trauma to the area. Another delayed complication is anesthesia dolorosa seen more commonly with alcohol and phenol neurolysis. Because the neurolytic block of the Gasserian ganglion is associated with myriad devastating complications, many neurosurgeons and pain medicine physicians choose to perform radiofrequency rhizotomy of the ganglion instead.[30] The technical difficulty and complications associated with Gasserian ganglion block led some investigators to perform peripheral branch (supraorbital, infraorbital, and mandibular nerves) injections with 10% phenol to relieve the pain of tic douloureux.[31]

Other Neurolytic Blocks of the Head and Neck

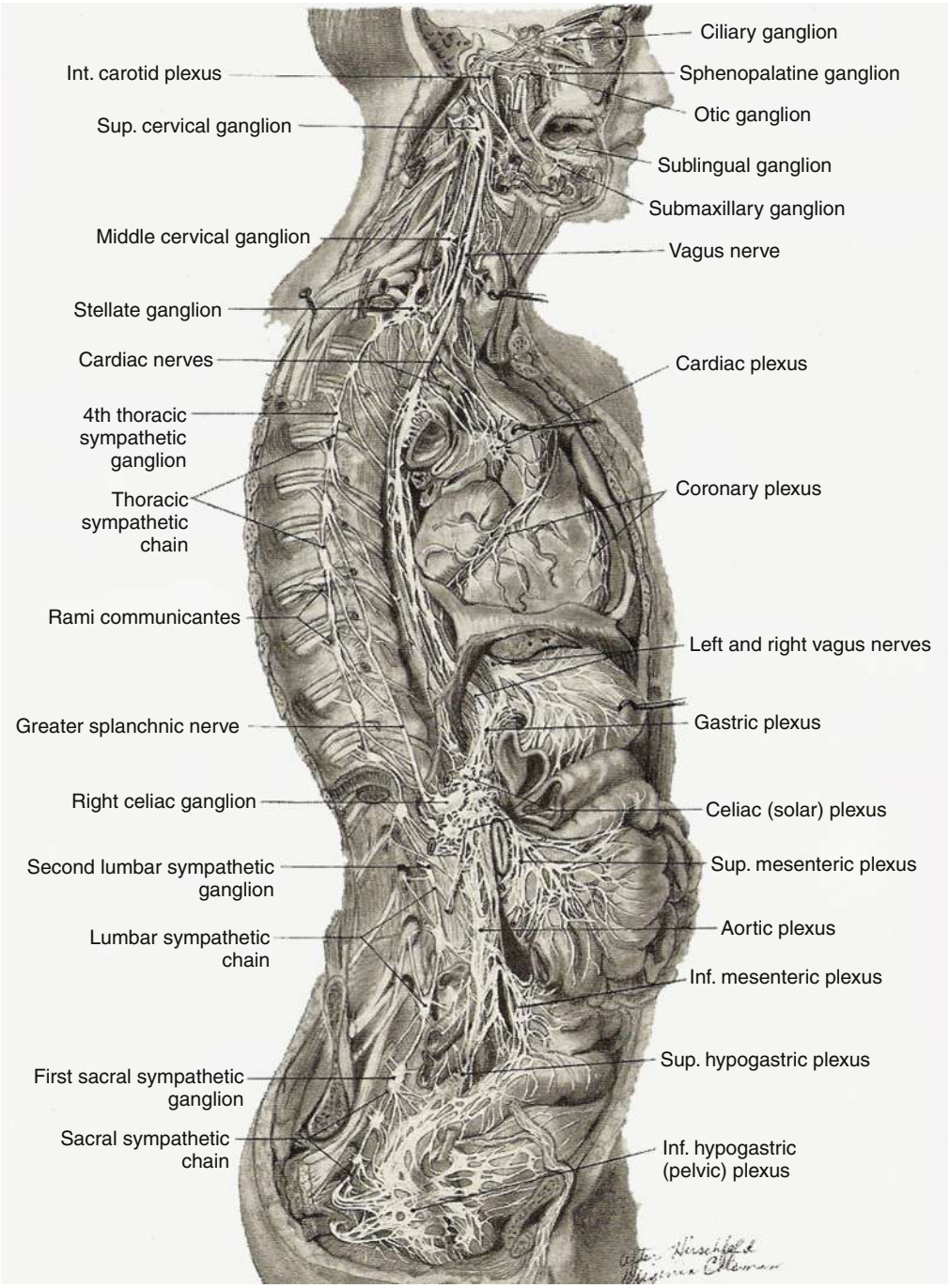
Neurolytic blocks of individual cranial nerves and their branches have also been performed, and complications are related to nerve location and the tissues it innervates. Neurolytic block of the maxillary nerve at the foramen rotundum or of the infraorbital nerve may cause ulceration and sloughing of the alar of the nose and the cheek, ischemic necrosis of the palate, or sloughing of the posterior portion of the superior ridge of the maxilla.[30] Blockade of the mandibular nerve at the foramen ovale may result in weakness of the muscles of mastication in the blocked side, whereas blockade of the facial nerve causes weakness or paralysis of the facial muscles. Blockade of the glossopharyngeal nerve is rarely performed because of the proximity of the nerve to the vagus, spinal accessory, and hypoglossal nerves. The close location of the other nerves led investigators to recommend blockade of the glossopharyngeal nerve under fluoroscopic control[32] or to use radiofrequency rhizotomy.[33] The sensory area of innervation of the glossopharyngeal nerve includes the nasopharynx, eustachian tube, uvula, tonsil, soft palate, base of the tongue, and part of the external auditory canal.[1] Paralysis of the pharyngeal muscles is a consequence of blockade of the glossopharyngeal nerve.

Paravertebral Sympathetic Neurolysis

Stellate Ganglion Block and Neurolysis

Clinically Relevant Anatomy

The cervical sympathetic trunk contains the superior, middle, and inferior cervical ganglia. In 80% of the population, the lowest cervical ganglion is fused with the first thoracic ganglion, forming the cervicothoracic (stellate) ganglion. The cervical sympathetic chain lies anterior to the prevertebral fascia, which encloses the prevertebral muscle (Fig. 63.2). The sympathetic chain is enclosed within the alar fascia, a thin fascia that separates the cervical sympathetic chain from the retropharyngeal space. The carotid sheath is connected to the alar fascia by a mesothelium-like fascia. The fascial plane that encloses the sympathetic chain may be in direct communication with several spaces and structures, including the brachial plexus, vertebral artery, endothoracic fascia, and the thoracic wall muscle at T1–T2. At the C6 level, the cervical sympathetic

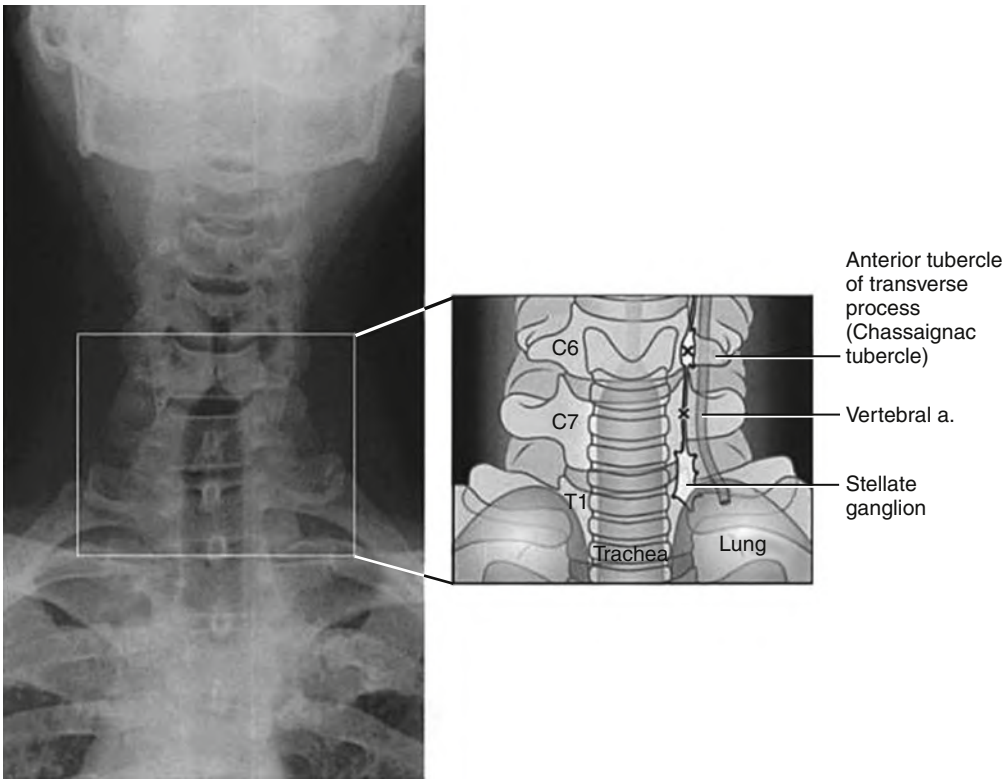


• **Figure 63.2** The peripheral autonomic nervous system. (From Bonica JJ. *The Management of Pain*. Philadelphia: Lea & Febiger; 1953.)

trunk is located posterolaterally to the prevertebral fascia on the surface of the longus colli muscle (LCM).[34] The carotid vessels are anterior, whereas the nerve roots that contribute to the inferior portion of the brachial plexus are lateral to the ganglion. The vertebral artery passes over the ganglion and enters the vertebral foramen posterior to the anterior tubercle of C6. The communications of the fascia covering the stellate ganglion with several structures, as noted previously, and the proximity of the stellate ganglion to the vertebral and carotid vessels, phrenic nerve, and the recurrent laryngeal nerve explain some of the potential complications of the stellate ganglion block (Fig. 63.3).[35]

Indications

SGB is commonly used for the diagnosis and management of sympathetically mediated pain and vascular insufficiency of the upper extremity. In addition, more esoteric indications that have been advocated include the treatment of a variety of medical conditions, such as phantom pain, postherpetic neuralgia, cancer pain, cardiac arrhythmias, orofacial pain, and vascular headache.[7] Recently, cervical sympathetic blockade has been suggested as an effective method for prevention and treatment of cerebral vasospasm, hot facial flushes, and post-traumatic stress disorder.[36–38]



• **Figure 63.3** Stellate ganglion anatomy. The relative position of the stellate ganglion, the vertebral artery, and the inferior cervical vertebrae. The relative positions of the C6, C7, T1 vertebral bodies of the Chassaignac tubercle (anterior tubercle of C6 transverse process) and the vertebral artery are illustrated. The vertebral artery traverses within the bony foramen at the C6 level, but the presence of a bony foramen at C7 is variable, and here the artery often courses unprotected anterior to the C7 transverse process. (Adapted from Janik IE, Hoeft MA, Rathmell J. Anatomic variation of Chassaignac tubercle measured by computed tomography: implications for stellate ganglion block. Presented at the annual fall meeting of the American Society of Regional Anesthesia and Pain Medicine; November 7-10, 2002, Phoenix, AZ; and Rathmell JP. Atlas of image-guided intervention in regional anesthesia and pain, 2005, Figure 10-2.) Rathmell JP; Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine, Lippincott Williams and Wilkins: Philadelphia, 2005; Figure 10-2.

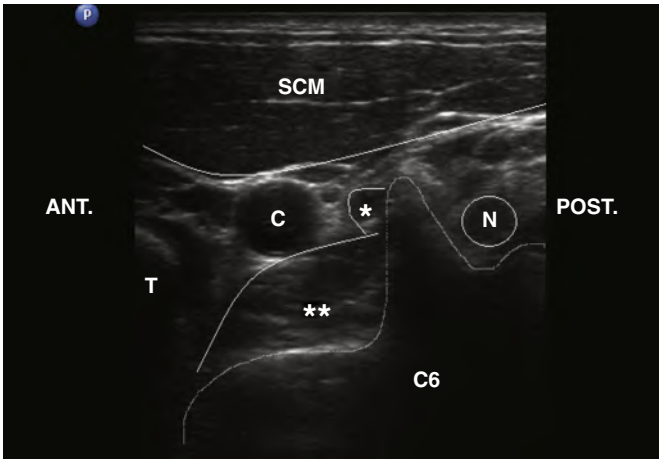
Available Techniques

Several techniques of stellate ganglion block have been described. These include insertion of the needle at the level of C6, placement of the needle at C7, and the posterior thoracic approach.[35] With C6 placement, the needle is placed in contact with either the C6 tubercle or the junction between the C6 vertebral body and the tubercle (Fig. 63.4). The needle is withdrawn 1–2 mm, and an initial test dose of 0.5–1 mL is injected, or volumes of 5–10 mL can be injected. If the patient is positioned in reverse Trendelenburg, the injectate travels caudad and reaches the stellate ganglion and the upper thoracic sympathetic ganglia.[36] A smaller volume of drug is adequate when the needle is placed at the level of C7. However, there is an increased incidence of vertebral artery injection with this approach because the artery lies anterior to the C7 transverse process. There is also an increased risk of pneumothorax because the dome of the lung is closer to the injection site. These risks are reduced when an oblique approach aiming at the uncinate process of C7 is taken.[37,38] The posterior thoracic approach requires fluoroscopic guidance to identify the lamina of T1 or T2, and dye injection is recommended to document the spread of the drug. In this approach, the needle contacts the lamina of T1 or T2, is moved laterally off the lamina, and is advanced to pass the costotransverse ligament at a depth of 2 cm beyond the lamina. Either loss of resistance is used, or dye is injected to confirm proper needle placement.

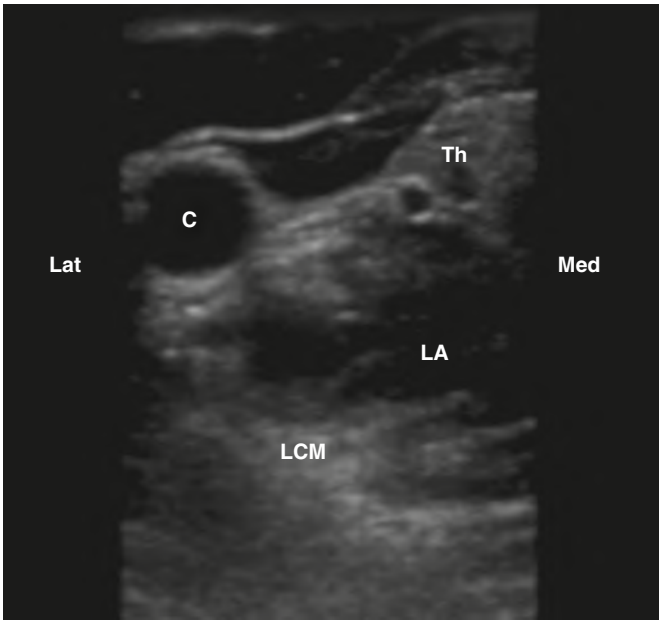
• **Figure 63.4** Anteroposterior fluoroscopy shows a block needle placed at the anterior base of the C6 transverse process. Injected contrast material is seen within the longus colli muscle.

Kapral published an ultrasound guided technique involving the use of ultrasound to visualize the stellate ganglion.[39] Since the initial technique was developed, many modifications have been made to increase the safety, efficacy, and speed of the block.[34,40] The patient is positioned supine with the neck slightly hyperextended, and an ultrasound probe is placed at the level of C6, providing a cross-section of the anatomy at this level (Figs. 63.5–63.6). Visible are the trachea, esophagus, thyroid gland, carotid artery, jugular vein, LCM, and transverse process of C6. A 22G × 2 inch needle can be advanced in plane with the ultrasound probe paratracheally toward the LCM while avoiding the other structures and stopping once the tip reaches the prevertebral fascia. The needle is inserted under continuous ultrasound guidance and directed to the anterior surface of the LCM via a short-axis, out of plane approach. When the tip of the needle is visualized, either directly or indirectly (tissue movement) as the target is approached, 1–2 mL of saline is injected to confirm the placement of the needle under the prevertebral fascia and facilitate clear separation of the tissue planes (Fig. 63.7). If the injectate is observed above the fascia or within the muscle, the needle must be carefully repositioned. If the spread is appropriate, 5–10 mL of local anesthetic is deposited under direct visualization and can be seen spreading along the prevertebral fascia.[41]

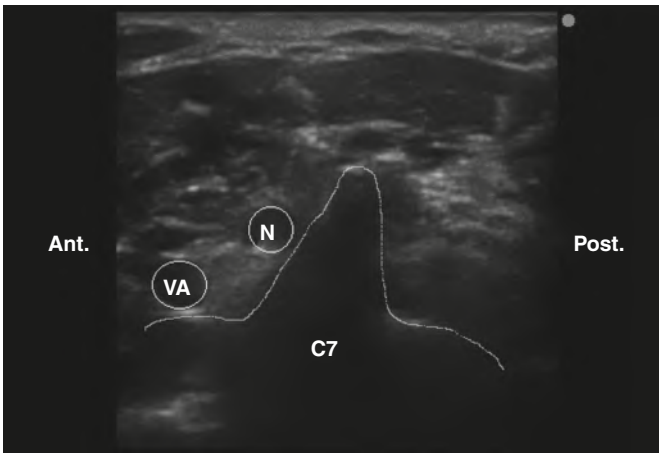
A lateral approach has recently been described and validated.[22] The patient is placed in the lateral decubitus position with the side to be treated uppermost. Preparation and ultrasonography are performed as described previously. The ultrasound transducer is centered on the C6 transverse process and not the anterior aspect of the neck. With the transducer placed as shown in Fig. 63.8, only the anterior tubercle of the C6 transverse process is visible adjacent to the projected entry point of the needle, and no visceral or neural elements are present between the entry site and the anterolateral surface of the LCM. The needle track is entirely intramuscular and passes through the sternocleidomastoid muscle, the anterior scalene muscle, or both. The internal jugular vein is occasionally seen within the projected needle track,



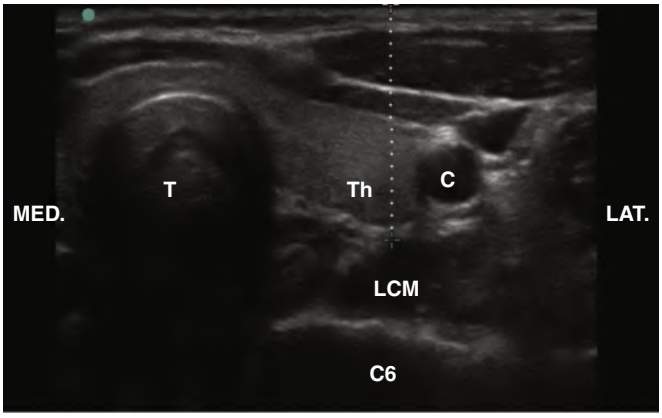
• **Figure 63.5** Short-axis view at the C6 level. *Asterisk*, Longus capitis muscle; *two asterisks*, longus colli muscle; *C*, carotid artery; *C6*, sixth cervical vertebra with a prominent anterior tubercle. *N*, C6 nerve root; *SCM*, sternocleidomastoid muscle; *T*, trachea.



• **Figure 63.7** Injection of local anesthetic produced an anechoic signal. After injection, the longus colli muscle *(LCM)* appears hyperechoic. *C*, Carotid artery; *Th*, thyroid.



• **Figure 63.6** Short-axis view at the C7 level. *C7*, Seventh cervical vertebra with only one tubercle; *N*, C7 nerve root; *VA*, vertebral artery.



• **Figure 63.8** Anterior ultrasound-guided approach. The *dotted line* represents the needle trajectory; it is trespassing through the thyroid *(Th)*. *C*, Carotid artery; *C6*, sixth cervical vertebra; *LCM*, longus colli muscle; *T*, trachea.

but it can readily be collapsed by placing light pressure on the transducer.

Skin anesthesia is performed immediately posterior to the ultrasound transducer. Under continuous ultrasound guidance, the needle is inserted via a short-axis, in plane technique (Fig. 63.9). The advantage of the lateral approach, besides avoiding trespassing through the thyroid, is totally controllable, visible progression of the needle from the skin entry point to the target. Verification of needle position and performance of the rest of the procedure are the same as the anterior approach.

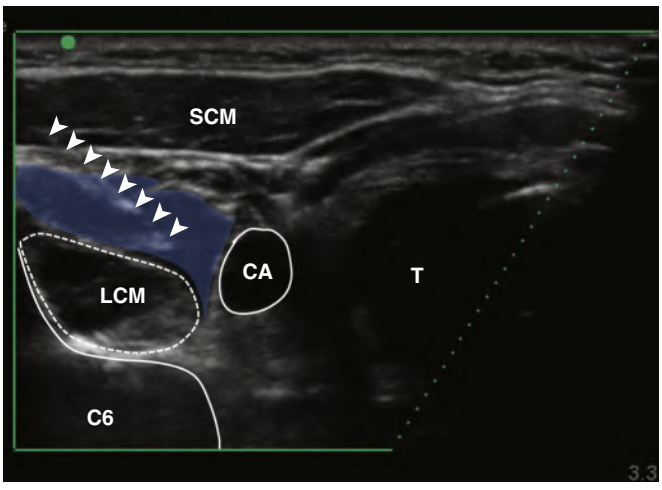
Injection of 5 mL of a local anesthetic typically results in C3-T1 prevertebral spread and complete blockade of the CST and stellate ganglion. If anesthetic blockade of the upper cervical ganglion is not desirable, it would be prudent to limit the volume of the injectant to 3 mL.

Complications

Blind paratracheal injection produces unreliable results and is associated with various side effects and complications, such as intravascular injection, formation of hematomas, temporary paralysis of the recurrent laryngeal nerve, diskitis, and esophageal injury.[39-44] Narouze and associates further emphasized the risks inherent with a blind approach[43] by pointing out that blind injection at the C6 level on the left side may cause inadvertent esophageal puncture or may traverse the thyroid.

Fluoroscopic guidance may prevent adverse outcomes related to intravascular, nerve root, or neuraxial injection. However, visualization of the soft tissue, vessels, and cervical sympathetic ganglia makes guidance with ultrasound superior to fluoroscopic guidance. Subfascial injection of 5 mL of an injectant reliably produces cervical sympathetic blockade. Ultrasound guidance may prevent the complications and adverse outcomes associated with either blind or fluoroscopically guided techniques.

The complications of intravascular injection of local anesthetic are well known. These include loss of consciousness, apnea, hypotension, and seizures. Local anesthetic blocks of the stellate ganglion have been performed for complex regional pain syndrome, vascular insufficiency of the upper extremities, and hyperhidrosis of the face and upper extremities. Neurolytic blockade of the stellate ganglion has been performed for complex regional pain syndrome when there is consistent relief after diagnostic block with local anesthetic and without prolongation of the duration of pain relief. The overall incidence of complications is 0.17%.[45] The exact incidence of pneumothorax is not known. Aside from Horner's syndrome, hoarseness, blockade of the brachial plexus, subarachnoid and epidural spread, and cord infarction have been reported.[46] Brachial plexus block is secondary to the needle being inserted too lateral or from the spread of the drug along the prevertebral fascia. Ptosis can be corrected by suspension operation of the upper eyelid. Additionally, retropharyngeal hematomas have been reported, ranging from minimal patient discomfort to complete loss of airway.[47,48] An unusual reported complication is transient locked-in syndrome, in which the patient is paralyzed and cannot breathe or speak but can only move their eyes because of accidental intravascular anesthetic injection.[49] These complications led other investigators to use alternative techniques to cervicothoracic sympathectomy, including radiofrequency rhizotomy and thoracoscopic sympathectomy.



• **Figure 63.9** Lateral ultrasound-guided approach. The needle *(arrowheads)* is placed under the prevertebral fascia. Local anesthetic *(semitransparent figure)* spread superficially to the longus colli muscle *(LCM)* and posteriorly to the carotid artery. C6, sixth cervical vertebra; SCM, sternocleidomastoid muscle; T, trachea.

Lumbar Sympathetic Neurolysis

Paravertebral sympathetic blocks are performed for the treatment of complex regional pain syndromes, vascular insufficiencies of the lower extremities, phantom limb pain, and other conditions such as hyperhidrosis. Percutaneous thoracic paravertebral sympathetic neurolysis is rarely performed because of the high incidence of pneumothorax. A thoracic surgeon who does a surgical sympathectomy under direct vision usually performs treatment of this region. Lumbar paravertebral sympathetic neurolysis can be more safely performed. In this technique, the needles are placed in the anterolateral surface of L2 or L3. Fluoroscopy is used to confirm the vertebral level of placement, correct position of the needle tip, and adequate spread of the dye along the anterolateral aspect of the vertebral bodies. Although a single needle technique can be used, two needles (one at L2 and the other at L3) are recommended for chemical neurolysis so that a smaller volume can be injected per needle. One to 2 mL of local anesthetic is injected, and if it is followed by a temperature increase, 3–4 mL of 6%–10% phenol is injected per needle. The reported complications of the block include subarachnoid injection secondary to injection near the dural cuff at the intervertebral foramen, sensory and motor block resulting from nerve root injury, paresthesia, and backache. The ureter can be injured from the needle or phenol-induced thrombosis of the branch of the ovarian artery supplying the ureter. Genitofemoral neuralgia occurs in 7%–20% of patients and may last four to five weeks.[50] Postsympathectomy dysesthesias result in numbness and pain in the thigh and may last several months. The use of guidance (fluoroscopy, computed tomography [CT], or ultrasound) is mandatory when neurolytic block of the sympathetic chain is performed. Alternate nonchemical neurolytic techniques, including radiofrequency rhizotomy of the lumbar sympathetic nerves, have been employed to avoid the complications from spillage of the neurolytic agent. However, this technique did not result in long-term relief,[51] although other studies have found benefits.[52,53] Compared with phenol neurolysis, incomplete neurolysis appears to be more common with radiofrequency rhizotomy,[54] but the incidence of postsympathectomy neuralgia was higher in the phenol group (33% vs. 11%).

Neurolytic Blocks of the Trunk and Extremities

Intercostal Neurolysis

Peripheral neurolysis is a controversial subject. Although some argue that it has no real use in pain management, it has found a role in intercostal neurolytic blocks for the management of malignant chest wall pain. The use of peripheral neurolysis follows successful diagnostic blocks using local anesthetics. Peripheral neurolytic blocks are frequently associated with neuritis and deafferentation pain, in addition to postinjection dysesthesias (Box 63.2). Although these complications are unpleasant, they may be preferable to the patient's current pain, or the patient may succumb to their primary disease before these complications fully manifest themselves.[55] Intercostal blocks are used in the treatment of thoracic or abdominal wall pain and as an adjunct in surgery.[56,57] Complications include pneumothorax, intravascular injection, intrapulmonary injection with consequent bronchospasm, and neuraxial spread (Table 63.2). The incidence of pneumothorax detected by radiograph is 0.082%–2%.[58] Clinically significant pneumothorax occurs at a low rate, and chest tube insertion is rarely required. Another reported complication is total spinal anesthesia after intraoperative intrathoracic injection.[59] The intrathoracic injection at a medial location resulted in the injection of the local anesthetic into a dural cuff or into the nerve itself, with the proximal spread of the drug. Bronchospasm from the intrapulmonary injection of phenol has been reported.[60] Persistent paraplegia from the intercostal block with 7.5% phenol has been reported, with the authors suspecting the damage occurred via the spread of phenol through the intervertebral foramen and subsequent destruction of motor and sensory nerve roots.[61] Similar to the advantages of its use in other peripheral nerve blocks, ultrasound has made intercostal nerve block a safer technique in that the pleura is visualized, preventing its puncture and avoiding pneumothorax.[62]

• Box 63.2 Limitations of Peripheral Neurolytic Blocks

- Motor deficits are likely when mixed sensory-motor nerves are blocked.
- Neuritis/deafferentation pain may occur and can be more severe than preexisting pain.
- Neurolytic blocks are not permanent.
- Sensory loss following peripheral neurolysis can, in some cases, become more distressing than the original pain.

TABLE 63.2 Complications After Truncal Blocks

Block	Complications
Intercostal	Pneumothorax
	Intravascular injection
	Bronchospasm (intrapulmonary injection)
	Neuraxial block
Somatic	Hypotension
	Urinary retention
Lumbar	Subarachnoid injection

Ilioinguinal and Iliohypogastric Neurolysis

Ilioinguinal and iliohypogastric nerve blocks are used in the perioperative management of pain after inguinal herniorrhaphy. Preoperative wound infiltration can decrease pain scores and analgesic requirements after inguinal herniorrhaphy. The preemptive analgesic effect of the preincisional infiltration of local anesthetic before herniorrhaphy has not been firmly established. In the pain clinic, ilioinguinal and iliohypogastric nerve blocks are performed in the diagnosis and treatment of inguinal and suprapubic pain after lower abdominal surgery or inguinal hernia repair. Complications of the block include unintentional blocks of the lateral femoral cutaneous and femoral nerves. The incidences of these complications are not known. Neurolytic blocks of these nerves are presently being supplanted by pulsed radiofrequency treatment (this is not a neurolytic procedure) and radiofrequency rhizotomy.[63] The advantage of radiofrequency techniques includes the ability to first stimulate the nerves to provide exact localization in a manner similar to sensory and motor testing of medial branch nerves in facet joint denervation. Diagnostic blocks are recommended before neurolytic (chemical or thermal) procedures are performed.

Neurolysis of Other Peripheral Nerves

Neurolytic injections have been reported to be useful in patients with palpable painful neuromas (0.2–0.5 mL of 5% phenol),[64] patients with poststernotomy pain secondary to scar neuroma (2–3 mL of 6% phenol),[65] and patients with painful surgical scars (1 mL of absolute alcohol).[66] Neuritis has not been reported after these peripheral neurolyzes.

Nerve root destruction in the extremities is rarely performed because of the attendant paralysis of the extremity. Mullin reported neurolytic blockade of the brachial plexus with 10 mL of 10% phenol in a patient with a painful arm secondary to Pancoast tumor.[67] The patient had short term pain relief with minimal motor blockade. The complications from neurolysis of peripheral nerves include painful dysesthesias and sensory and motor blockade. The exact incidences of these complications are not known but are high enough that this treatment is not recommended.

Neurolysis for Myofascial Pain and Spasticity

Neurolytic blocks of peripheral nerves are useful in patients with acquired spasticity to facilitate rehabilitation and restore the normal position of the limb for maintenance of hygiene. Examples of these blocks include obturator block to relieve hip adduction, musculocutaneous nerve block for elbow flexion, and posterior tibial nerve block for plantar flexion.[68] Peripheral nerve blocks with phenol have been performed in patients with spasticity to improve their gait and balance and assist in their rehabilitation. In this technique, the motor or mixed nerves are targeted preferentially. A nerve stimulator is used for nerve identification. Injections of small volumes of 3%–5% phenol are effective in relieving the hypertonicity of affected muscles, and relaxation of the muscle usually lasts two months. During this time, extensive physical therapy is employed for functional training of the limb. It appears that ethanol treatment can extend the therapeutic benefit. In a randomized controlled trial of 20 patients evaluating phenol (5%) versus ethanol (50%) in neurolysis of tibial motor branches for gastrocnemius spasm after stroke, ethanol maintained its effect for six months in nine of the 10 patients, whereas phenol lasted the same amount of time in seven of the 10 patients.[69] The reported complications include focal motor weakness in 15% of patients and dysesthesias in 10% of patients, but there were no differences

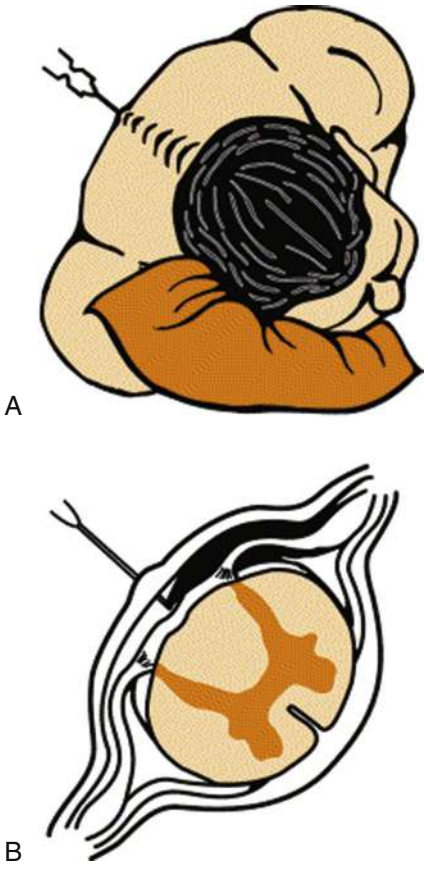
between those that received ethanol and those that received phenol. The motor weakness usually lasts one week, whereas the dysesthesias last several days to weeks. Others have reported a rare complication of arterial occlusion of the patient's upper limb after phenol block of the brachioradialis and musculocutaneous nerves.[70] Of note, the development and widespread use of botulinum toxin has made neurolysis a therapy of last resort for this condition.

Neuraxial Neurolysis

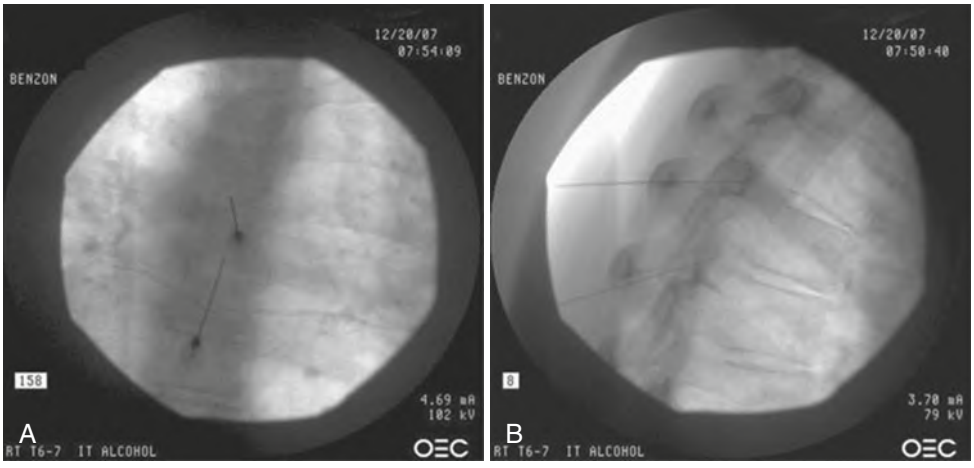
Intrathecal Alcohol

A neurolytic intrathecal procedure should be performed at the level where the targeted dorsal root leaves the spinal cord and not at the level where it passes through the intervertebral foramen. The latter is not recommended because of a mismatch of the spinal cord level and vertebral bone level (especially as one progresses from the thoracic spinal cord to the lower lumbar). An accurate determination of the level to be blocked should be evaluated according to dermatome and sclerotome charts, as well as selective local anesthetic intrathecal blockade.[71] The patient should be positioned laterally so that the rootlets (dorsal root entry zone [DREZ]) are above the injection site.[72] This positioning is necessary given that alcohol will float in the CSF because of its hypobaric nature.[73] The patient should also be turned 45 degrees toward the prone position (Fig. 63.10). This will raise the targeted area (DREZ) horizontally so it will be superior to the ventral nerve rootlets, and it makes contact with the neurolytic.[72] After proper patient positioning, a short beveled (e.g. small Touhy, 22-gauge) needle is placed into the predetermined level slowly until arriving at the epidural space. This is best confirmed using a loss of resistance to air and guided by fluoroscopy. After ascertaining that the epidural space has been reached, the needle should be advanced slowly while aspirating continuously until it reaches the intrathecal space and contrast dye administration (Fig. 63.11). The physician should then inject a low volume/high concentration of rapidly acting local anesthetic to provide anesthesia and clinical feedback of needle location. The lack of pretreatment with local anesthetic will result in significant discomfort and the possibility of patient movement. Using a 1 mL syringe, the alcohol is injected in 0.1 mL increments, with at least 60–90 s between repeat administrations. The maximum dose per nerve is usually 0.3 mL, and the total alcohol volume should not exceed 0.5–0.7 mL when several nerve roots are neurolyzed.[74]

After injection, the patient should remain in the same position for 15 to 30 min. This immobilization allows the alcohol to exert its maximal effect at the desired location, with minimal spread to



• **Figure 63.10** **A**, Proper positioning of a patient with left-sided pain for intrathecal alcohol injection. Note the 45 degree anterior tilt, intended to bathe the dorsal (sensory) nerve roots with hypobaric alcohol while sparing the ventral (motor) roots. **B,** Cross-sectional diagrammatic depiction of the above. (Reprinted with permission from Candido K, Stevens RA. Intrathecal neurolytic blocks for the relief of cancer pain. *Best Pract Res Clin Anaesthesiol*. 2003;17:407-428, Figure 4.)



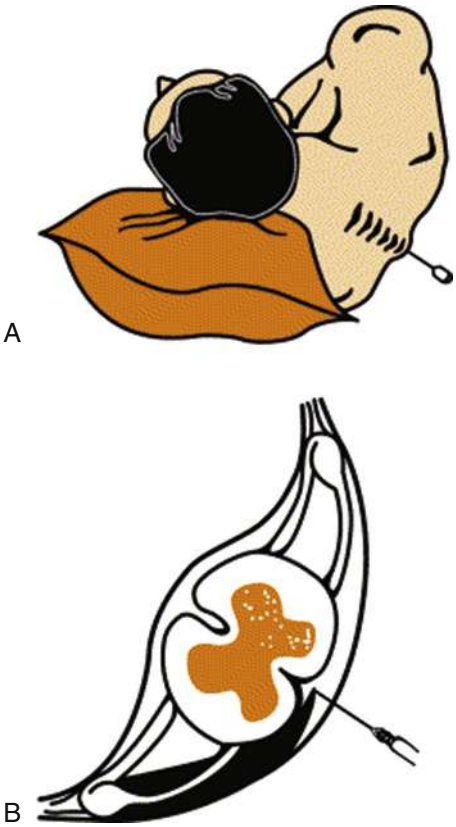
• **Figure 63.11** Intrathecal neurolysis. **A,** Anterior-posterior fluoroscopic view. **B,** Lateral fluoroscopic view. (Reprinted with permission from Benzon H, Raja S, Fishman S, et al. (eds). *Essentials of Pain Medicine. 3rd ed.* Philadelphia: Elsevier; 2011: Figure 72-3.)

adjacent levels. After the 30 min period, a neurologic exam should be performed. The patient's pain should be reassessed three to five days after the alcohol injection to determine the effectiveness of the procedure.

Intrathecal Phenol

The same considerations that occur prior to the injection of alcohol also apply to phenol. The pain location should be determined with dermatome and sclerotome mapping and isolated with a diagnostic injection of local anesthetic or contrast dye under fluoroscopy. There are two fundamental differences between alcohol and phenol administration. When using phenol, the patient's targeted anatomy must be facing down, the patient must be leaned 45 degrees supine, and the spinal needle diameter must be larger because of the increased viscosity of phenol. The hyperbaric nature of phenol in glycerin requires positioning so the phenol sinks to targeted DREZ and rootlets. A short, 20-gauge needle should allow the thick phenol solution to be injected in most situations. However, if this proves difficult, warming the injectate in a warm water bath before drawing may ease the flow of the injection.

Although positioning can be challenging, a common technique involves slightly elevating the head of the bed, with the bed under the target flexed and the patient turned 45 degrees supine (Fig. 63.12). Using supporting devices, such as pillows, towels, and foam, and a judicious amount of intravenous sedation can facilitate a reasonable level of comfort to prevent failure of the technique resulting from patient movement. Unlike alcohol, phenol does not require pretreatment with local anesthetic to provide analgesia of the site. However, the diagnostic value (needle localization) of the local anesthetic is still imperative. Similar to alcohol neurolysis, phenol is injected in 0.1 mL increments, with 60–90s between subsequent injections. Phenol is injected up to a total dose of 0.5–0.7 mL. The feeling of warmth from the phenol is fleeting and may provide some pain relief. Although there is less diffusion with phenol than alcohol, the patient should be maintained in position for 30 min after phenol administration. The full effect of phenol manifests over approximately 24 h.



• **Figure 63.12** **A,** Proper positioning of a patient with left-sided pain for intrathecal phenol in glycerin. Note the 45 degree posterior tilt, intended to bathe the dorsal (sensory) nerve roots with hyperbaric phenol while sparing the ventral (motor) roots. **B,** Cross-sectional diagrammatic depiction of the above. (Reprinted with permission from Candido K, Stevens RA. Intrathecal neurolytic blocks for the relief of cancer pain. *Best Pract Res Clin Anaesthesiol.* 2003;17:407-428, Figure 5.)

Epidural Neurolytic Block

Epidural neurolysis is used for abdominal cancer pain of both visceral and mixed somatic and visceral origin. Epidural neurolysis remains popular compared to intrathecal neurolysis because of its increased safety index, ease of repeated injections, and its greater efficacy on thoracic and cervicothoracic junction pain. However, it often provides less complete anesthesia of the patient's painful areas compared to intrathecal administration. Although the traditional technique is described in this chapter, one study demonstrated that the use of a transforaminal approach, when necessary, provided excellent results.[75] Selecting the appropriate size needle depends on the agent used, as discussed previously. If alcohol is used, the physician may use an epidural catheter for delivery. An epidural catheter approach provides advantages of repeated injections and can be performed without accessing the epidural space multiple independent times. However, the indwelling catheter can be an entry site for epidural infection. The most appropriate catheter to use is a soft-tipped styletted catheter that can be maneuvered with precision and allows confirmation of position with the injection of a small amount of contrast and local anesthetic.

Unlike the intrathecal administration of neurolytic agents, needle or catheter tip location should be chosen near the vertebral bone that corresponds to the dermatomal levels manifesting in the patient's pain area to deposit the medication over the appropriate nerve roots. The injections should be performed under sterile conditions. It has been recommended that injections be repeated over several days to improve efficacy and outcome. Once the needle and patient positioning have been established, contrast-enhanced fluoroscopic imaging and a local anesthetic test dose can be performed to confirm proper needle depth and location. The appropriate volume of injectate depends on the level of the neurolysis being performed. Doses ranging from 2–5 mL are usually adequate, with doses increasing as location moves more caudally. Racz and colleagues endorse daily injections until noticeable changes in pain levels no longer occur, or the patient is pain-free after 24 h. For up to three days after the initial placement of an epidural catheter 3–5 cm into the epidural space, ethanol can be injected daily. Before each daily administration, the researchers reconfirmed placement with a local anesthetic test dose.[76] Using 0.2 mL increments, they administered 3–5 mL of alcohol over 20–30 min. Although initial relief was achieved in all cancer patients, results are less significant in patients with chronic nonmalignant pain.[77] In four studies, the results of thoracic epidural neurolysis revealed a significant improvement in cancer pain.[6] Pain relief, ranging from 65%–100%, was achieved in 80% of patients. Pain relief varied among populations and reflected the severity of disease. Nonetheless, many patients were pain-free until their death. In the patients who survived, the duration of pain relief varied from less than one month to more than three months.

Neuraxial neurolytic procedures for cancer pain are now rarely used because intrathecal opioid pumps have supplanted it. Intrathecal medication infusion pumps have the advantage of managing pain from the progression of the disease or future sites of painful metastases, which are common occurrences in a patient with malignancy.

Other Complications Associated With Intrathecal and Epidural Neurolysis

Although ease of administration is a factor, there does not appear to be an increased margin of safety of epidural neurolysis compared to intrathecal neurolysis. A study by Katz showed that two weeks after the lumbar epidural injection of phenol in a group of primates, predominant posterior nerve root damage was noted, in addition to the anterior nerve root and spinal cord damage. These test subjects also demonstrated lower extremity motor weakness on physical examination.[78] Complications with neurolysis range in frequency from 1%–14%, and in severity between incomplete block to limb weakness or bladder/rectal paresis.[5] Like most interventional pain procedures, the most common complication is the failure of the procedure to provide significant pain relief. Poor pain relief can have numerous etiologies. It is not unusual for patients to have high expectations for pain relief and have those expectations not met by neurolysis. Therefore the pain physician needs to have clear communication and discuss rational expectations with the patient prior to the procedure to prevent these disappointments. Another cause of inadequate pain relief may be as simple as an incomplete block that can be remedied with a repeat dose. If tumor growth is extensive or crosses several dermatomes, neurolysis may be less effective. Unfortunately, there is always the possibility that the block works well, but that local spread of the neurolytic agent may have produced peripheral damage.

There are complications because of entry into the anatomic space where these medications are administered. They include postdural puncture headache, meningitis, arachnoiditis, and neural damage from trauma. Postdural headaches usually resolve quickly, within one to five days. Complications related to neurolytic agents include loss of motor function because of neurolysis of the ventral rootlets, loss of touch and proprioception, and loss of sphincter tone. Of these potential complications, loss of bowel or bladder sphincter tone is relatively common. The complications resulting from the neurolytic agents are usually transient. According to Gerbershagen, who observed the duration required for resolution of neurolytic complications, 28% resolved within three days, 23% within one week, 21% within one month, 9% within four months, and 18% longer than four months.[79] Complication rates appear to be similar between alcohol and phenol as shown by Swerdlow, who analyzed complications in a series of 145 patients.[80]

Complications can be specific to the location along the spine where the neurolysis is performed. At the cervical level, damage can occur to the brachial plexus, most often manifesting as limb paresthesia. Complications at the thoracic level are the least common relative to the cervical and lumbar level. Below the L1 spinal level, injections may travel into the cauda equina, where anterior and posterior roots are not separated. This factor may make the degree of motor or sensory effect difficult to predict.

Changes in opioid use may occur after a neurolytic block. Patients who have typically been on high doses of opioids for long periods will have reduced requirements for pain control with successful neurolysis. Rapid discontinuation of opioids will cause withdrawal side effects; without pain as a stimulus, pre-neurolysis opioid doses may produce excessive sedation and respiratory depression. Careful observation of the patient in the hours to days post successful neurolysis can circumvent these problems.

Neurolysis of the Sympathetic Axis for Cancer Pain Management

Celiac Plexus Block

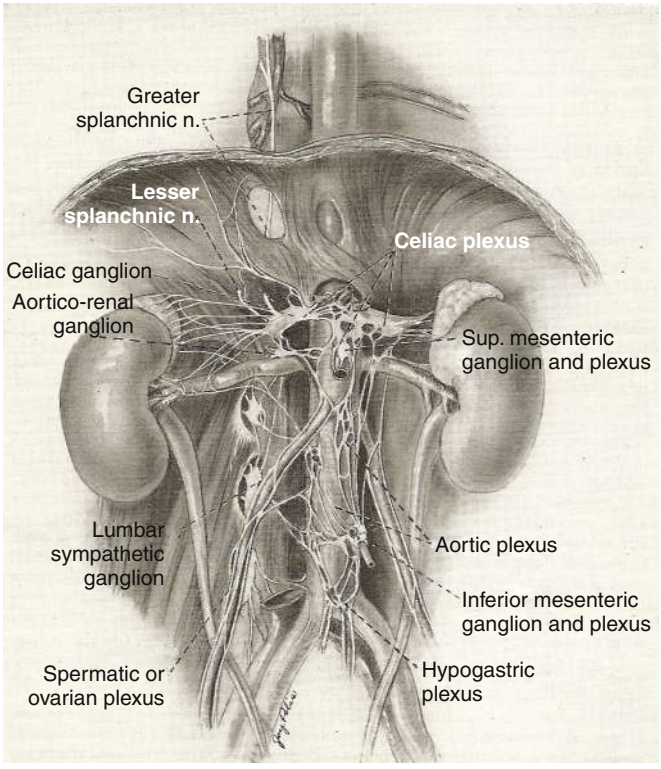
Clinically Relevant Anatomy

The celiac plexus is situated retroperitoneally in the upper part of the abdomen. It is at the level of the T12 and L1 vertebrae, anterior to the crura of the diaphragm. The celiac plexus surrounds the abdominal aorta and the celiac and superior mesenteric arteries (Fig. 63.13). The plexus is composed of a network of nerve fibers from both the sympathetic and parasympathetic systems. It contains two large ganglia that receive sympathetic fibers from the three splanchnic nerves (greater, lesser, and least). The T5–T9 preganglionic fibers coalesce to form the greater splanchnic nerve; T10 and T11 constitute the lesser and T12 the least splanchnic nerves.[81]

The plexus also receives parasympathetic fibers from the vagus nerve. Autonomic nerves supplying the liver, pancreas, gallbladder, stomach, spleen, kidneys, intestines, and adrenal glands, as well as blood vessels, arise from the celiac plexus. The sensory (afferent) fibers do not synapse in the plexus but rather traverse it and ascend to spinal levels through the splanchnic nerves.

Indications

Neurolytic celiac plexus block (NCPB) has been used for malignant and chronic nonmalignant pain. NCPB is indicated for the management of pain related to cancer of the pancreas, stomach, duodenum, and proximal part of the small bowel. In addition, metastatic tumors in the lymph nodes may cause similar pain and might be amenable to NCPB. In the case of benign conditions,



• **Figure 63.13** Celiac plexus anatomy (From Bonica JJ. *The Management of Pain*. Philadelphia: Lea & Febiger; 1953.)

analgesic prognostic CPB is performed and may be repeated as needed. Alternatively, if the reduction in pain was significant but lasted only short term, NCPB may be attempted.

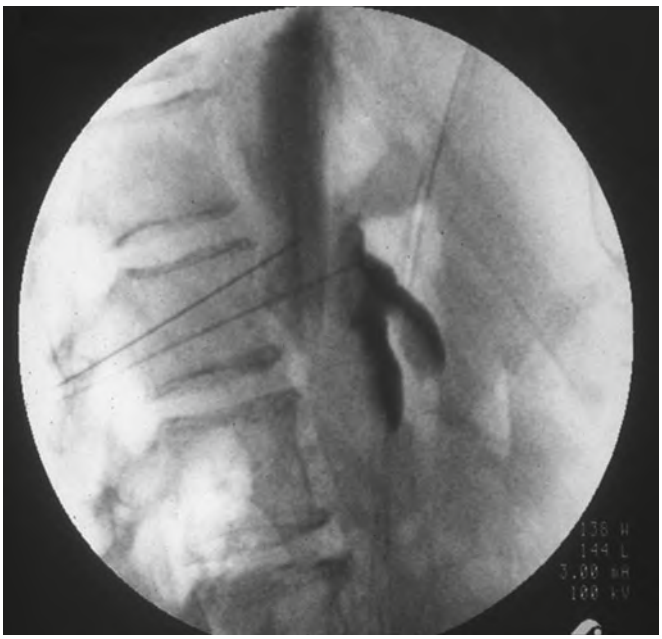
In patients with acute or chronic pancreatitis, celiac plexus block has been used with variable success.[82] Likewise, patients with upper abdominal cancer who have a significant visceral pain component have responded well to this block.[83]

Evidence for Celiac Plexus Block

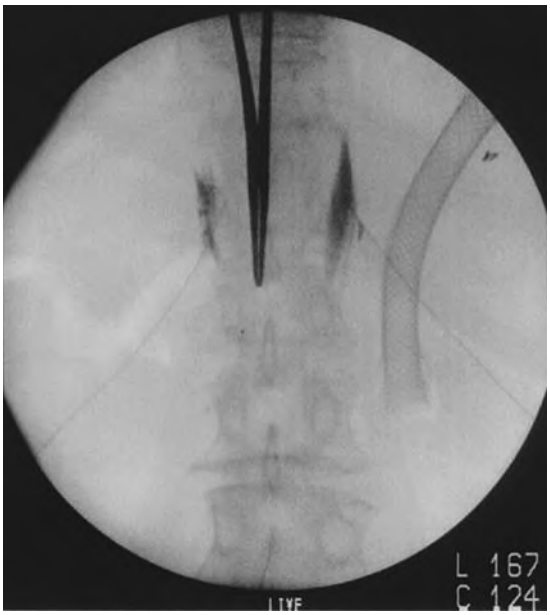
The Cochrane collaboration performed a systematic review of all randomized controlled studies investigating the effectiveness of celiac plexus block in the management of pancreatic cancer pain. They concluded that despite a small amount of evidence for an increase in pain relief, the improved side effect profile because of the reduced need for opiates is desirable.[84] It must be considered that many of the studies comparing the various interventional procedures with oral pharmacotherapy included NSAIDs. If more protocols in the future exclude NSAIDs, there may become a bigger statistical difference between the interventional and pharmacotherapy groups. A randomized, controlled study showed that CPB was effective in treating feeding intolerance in patients with critical illness when intravenous drug therapy failed to improve gastrointestinal dysfunction.[85]

Available Techniques

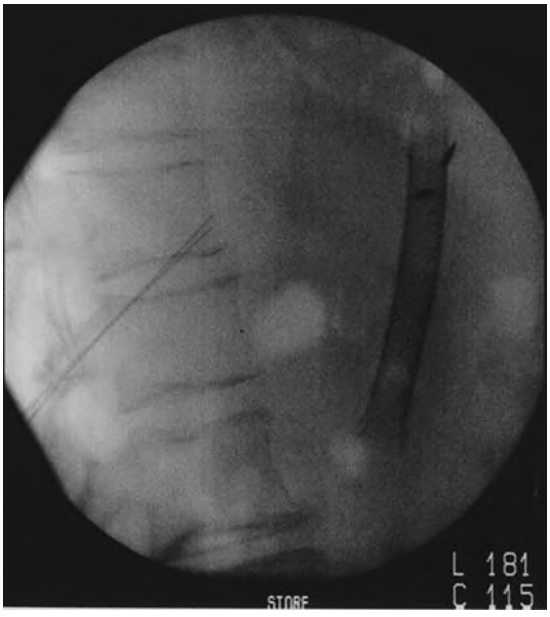
Three approaches to block nociceptive impulses from viscera in the upper abdominal region include the retrocrural (or classic) approach, the anterocrural approach, and neurolysis of the splanchnic nerves.[86–89] Regardless of the approach, the needle or needles are inserted at the level of the first lumbar vertebra, 5–7 cm from the midline. Then the tip of the needle is directed toward the upper third of the body of L1 for the retrocrural and toward the lower third of the body of L1 for the anterocrural technique (Fig. 63.14). In the case of the retrocrural approach, the tip of the needle is advanced no more than 0.5 cm anterior to the anterior border of L1, and with the anterocrural approach (Fig. 63.14), the tip of the needle is advanced through the aorta on the left side until no more blood flow is noted through the needle. This is why the anterocrural approach is also known as the transaortic approach. In the case of a splanchnic nerve block, the needle is directed toward the body of T12 (Fig. 63.15). In this case, perfect needle positioning is achieved when the tip of the needle is at the anterior portion of the T12 vertebral body on the lateral view (Fig. 63.16).



• **Figure 63.14** Neurolysis of the celiac plexus, retrocrural versus anterocrural positions of the tip of the needle on the lateral view. Note that for a retrocrural technique, the tip of the needle is in the upper third of L1 and about 1 cm beyond its anterior border. The spread of the contrast medium is cephalad. The tip of the needle is in the lower third of L1 and about 3 cm beyond its anterior border for an anterocrural technique. In this case, the spread of contrast medium occurs caudad.



• **Figure 63.15** Neurolysis of the splanchnic nerves with needle position on the anteroposterior view. Note that the spread of the contrast medium is limited to the lateral portion of T12.

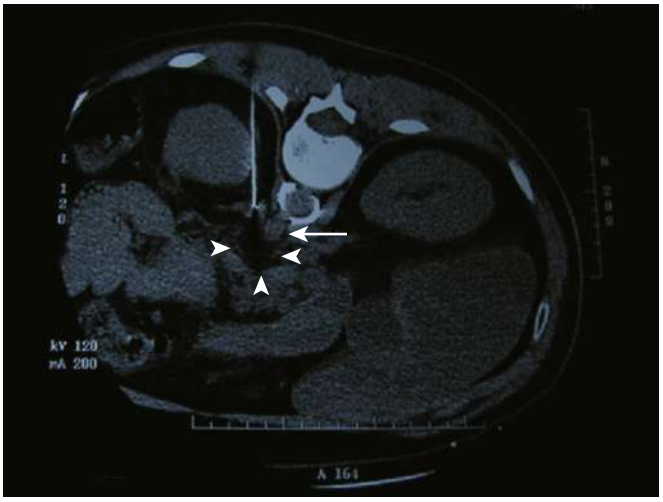


• **Figure 63.16** Neurolysis of the splanchnic nerves with needle position on the lateral view. Note that the tip of the needle is advanced until it is at the same level of the anterior border of T12 to avoid potential puncture of the pleura.

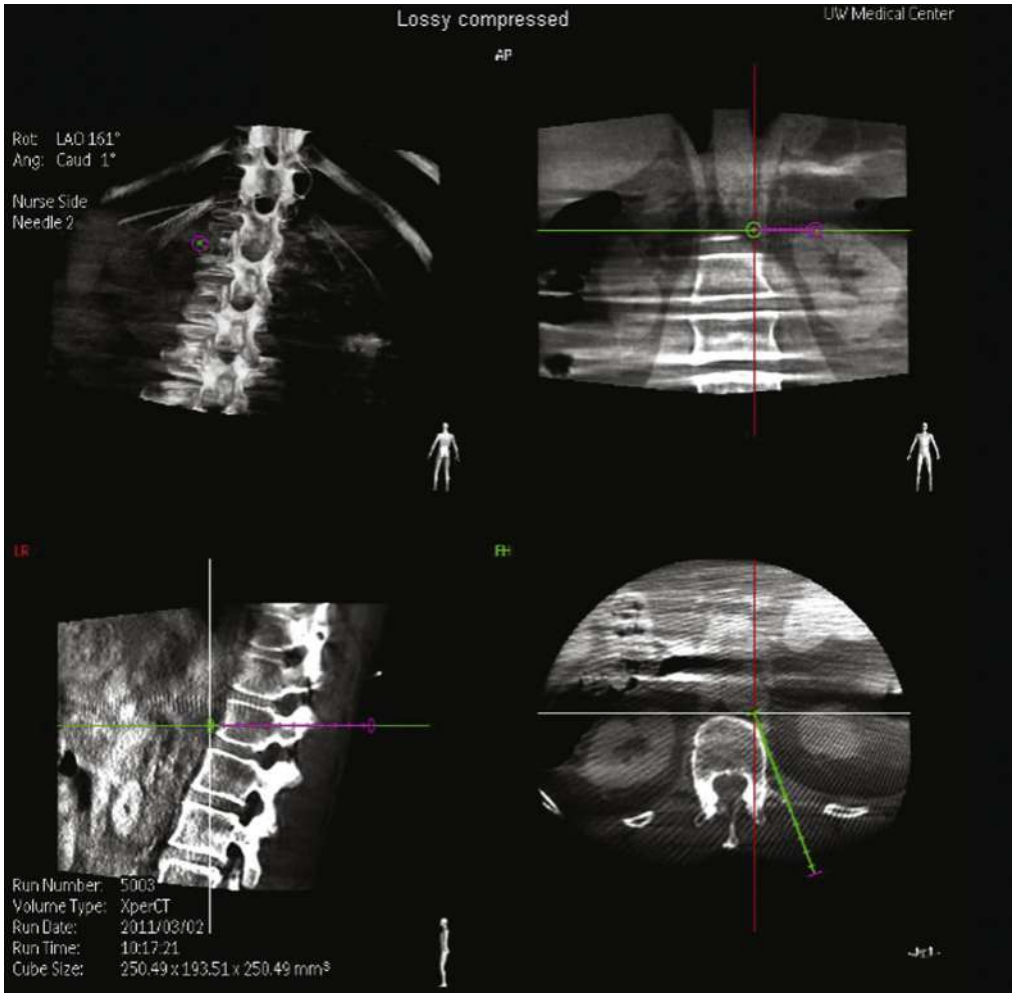
CT (Figs. 63.17 and 63.18.) and ultrasound techniques (Figs. 63.19.14–63.21) have allowed pain specialists to perform neurolysis of the celiac plexus via a transabdominal approach. This approach is frequently used when patients cannot tolerate either the prone or lateral decubitus position or when their liver is so enlarged that a posterior approach is not feasible. CT guidance allows an anterocrural technique to be performed without piercing the aorta, thus adding an element of safety in this case (see the section "Complications"). Ultrasound guided percutaneous CPB may have several benefits compared to other modalities. It may be performed at the bedside and has no radiation hazards. In addition, the supine position is more comfortable for patients. It allows real-time visualization of the spread of the injectant. Its disadvantages include poor visualization of deeper structures, including the pancreas, and interference by air in the intestinal loops. Similar to anterior CT guidance, it may be associated with perforation of the stomach, intestine, pancreas, or liver.

Drugs and Dosing

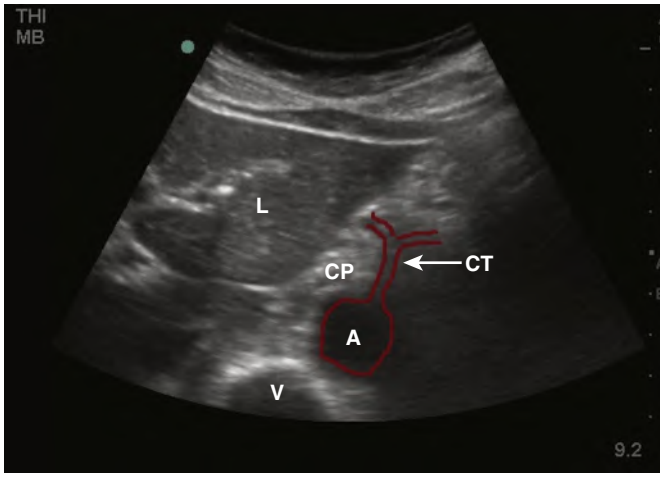
For neurolytic blocks performed via the retrocrural or anterocrural approaches, 50%–100% alcohol is used. Injected by itself, alcohol can produce severe pain. Thus it is recommended that 5–10 mL of 0.25% bupivacaine first be injected 3–5 min before injection of the alcohol or at the time of the injection by diluting 100% alcohol to a 50% concentration with the same amount of local anesthetic (0.25% bupivacaine). Phenol in a 6% to 10% final concentration may also be used; it has the advantage of being painless on injection, and both agents seem to have the same clinical efficacy. The



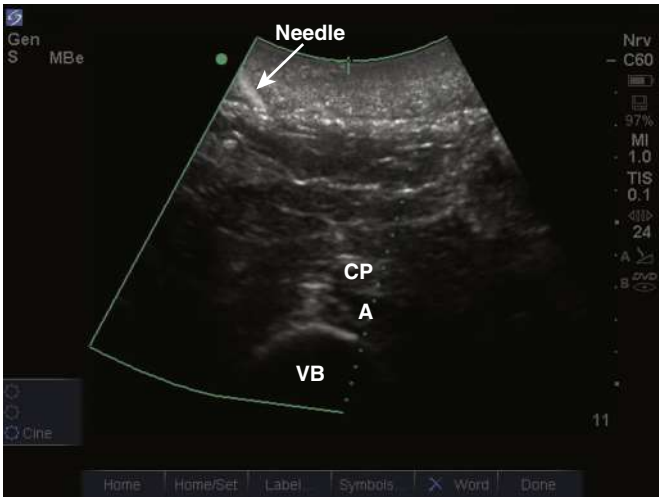
• **Figure 63.17** Computed tomography-guided celiac plexus block. The needle is positioned adjacent to the aorta, and alcohol is injected (the *arrowheads* are pointing to the *black shadow*). The *arrow* indicates the celiac trunk.



• **Figure 63.18** Procedural planning with cone-beam computed tomography.



• **Figure 63.19** Short-axis ultrasound view. *A*, Aorta; *CP*, celiac plexus; *CT*, celiac trunk; *L*, liver; *V*, L1 vertebral body.



• **Figure 63.21** Needle inserted in plane in a short-axis view and placed onto the celiac plexus *(CP)*. *A*, Aorta; *VB*, vertebral body.

• **Figure 63.20** Long-axis ultrasound view. *A*, Aorta; *arrow*, superior mesenteric artery; *arrowhead*, celiac trunk.

dose of alcohol or phenol administered varies with the approach to be used. For the retrocrural approach, 20–25 mL of alcohol is injected on each side. Consequently, the need to inject this high volume precludes the use of phenol in the retrocrural approach. For the anterocrural approach, 8–10 mL of either neurolytic agent is used per side. For splanchnic nerve blocks, 6–8 mL of phenol per side is recommended.

Complications

The incidence of complications from NCPBs was evaluated by Davis[90] in 2730 patients who had blocks performed from 1986–1990. The overall incidence of major complications (e.g. paraplegia, bladder, and bowel dysfunction) was one in 683 procedures. However, the report does not describe which approach or approaches were used to perform the blocks.

Complications associated with celiac plexus block appear to be related to the technique used: retrocrural,[87] transcrural,[88] or transaortic.[89] In a prospective, randomized study of 61 patients with cancer of the pancreas, Ischia and colleagues[86] compared the efficacy and incidence of complications associated with these three approaches with those of celiac plexus neurolysis. Orthostatic hypotension occurred more often when the retrocrural (50%) or splanchnic (52%) technique was used, thus suggesting associated neurolysis of the sympathetic chain. In contrast, the anterocrural approach produced a 10% incidence of hypotension. Conversely, transient diarrhea was more frequent with the anterocrural approach (65%) than with the splanchnic nerve block technique (5%) or the retrocrural approach (25%). The incidence of dysesthesia, interscapular back pain, reactive pleurisy, hiccups, or hematuria was not statistically different among the three groups.

The following paragraphs discuss several aspects involved in the diagnosis and management of specific complications.

Malposition of the needle is avoided with radiologic imaging before injection of a neurolytic agent in as much as the tip of the needle may be intravascular, in the peritoneal cavity, or in a viscus. Imaging guidance techniques currently used include biplanar fluoroscopy, CT, and ultrasound. However, no study has evaluated the superiority of one technique over the others. Wong and Brown[91] suggested that the use of radiologic imaging does not alter the quality of the block or the incidence of complications based on a retrospective study of 136 patients with pancreatic cancer pain treated with a celiac plexus block with or without radiologic control of the position of the tip of the needle. However, it is not clear how many of these patients underwent radiologic imaging. Assuming that half the patients did not, the upper 95% confidence limit for complications would be 5%.[92]

Orthostatic hypotension may occur up to five days after the block. Treatment includes bed rest, avoidance of sudden changes in position, and replacement of fluids. Once the compensatory vascular reflexes are fully activated, this side effect disappears. Wrapping the lower extremities from the toes to the upper part of the thighs with elastic bandages has been successful in patients in whom orthostatic hypotension developed and thus enabled them to walk during the first week after the block.

Backache may result from local trauma during needle placement and subsequent retroperitoneal hematoma or from irritation of retroperitoneal structures by alcohol. Patients with a backache should have at least two hematocrit measurements at a 1 h interval. If there is a decrease in the hematocrit, radiologic imaging is indicated to rule out a retroperitoneal hematoma. Urinalysis positive for red blood cells suggests renal injury.

Retroperitoneal hemorrhage is rare. However, in patients with orthostatic hypotension, the possibility of hemorrhage must be ruled out before assuming that it is a physiologic response to the block. Patients with backache and orthostatic hypotension develop after a celiac plexus block should be admitted to the hospital for serial hematocrit monitoring. If the hematocrit level is low or decreasing, patients should undergo radiologic evaluation to rule out injury to the kidneys, the aorta, or other vascular structures. Surgical consultation should be obtained as soon as feasible.

Diarrhea may occur as a result of sympathetic block of the bowel. Treatment includes hydration and antidiarrheal agents. Oral loperamide is a good choice, although any anticholinergic agent may be used. Matson and colleagues[93] reported nearly fatal dehydration from diarrhea following this block. In debilitated patients, diarrhea must be treated aggressively.

Abdominal aortic dissection has also been reported.[94,95] The mechanism of aortic injury is direct damage with the needle during the performance of the block. As expected, the anterocrural approach is more frequently associated with this complication. Thus this approach should be avoided in patients with atherosclerotic disease of the abdominal aorta.

Paraplegia and *transient motor paralysis* have occurred after celiac plexus block.[96–102] These neurologic complications may be because of spasms of the lumbar segmental arteries that perfuse the spinal cord.[103] In fact, canine lumbar arteries undergo contraction when exposed to both low and high concentrations of alcohol.[103] Thus these data suggest that alcohol should not be used if there is evidence of significant atherosclerotic disease of the aorta because the circulation to the spinal cord may also be impaired and be dependent only on lumbar artery flow. However, there is also a report of paraplegia after the use of phenol,[96] which suggests that other factors (e.g. direct vascular or neurologic injury or retrograde spread to the spinal cord) may come into play. These complications further support the need for radiologic imaging when performing these blocks.

Efficacy

Three randomized controlled trials[86,104,105] and one prospective study[106] have evaluated the efficacy of celiac plexus neurolysis in relieving pain caused by upper abdominal cancer. In a prospective, randomized study, Ischia and coworkers[86] evaluated the efficacy of three different approaches to celiac plexus neurolysis for pancreatic cancer. Of 61 patients with pancreatic cancer pain, 29 (48%) experienced *complete* relief of pain after the neurolytic block. The remaining 32 patients (52%) required further therapy for residual visceral pain secondary to technical failure in 15 patients and neuropathic or somatic pain in 17 patients. The second trial,[104] which compared the procedure with oral pharmacologic therapy in 20 patients, concluded that celiac plexus neurolysis results in an equal reduction in visual analog scale (VAS) pain score as does therapy with a combination of NSAIDs and opioids. However, opioid consumption was significantly lower in the group of patients who underwent neurolysis than in the group receiving oral pharmacologic therapy during the seven weeks of the study. The incidence of side effects was greater in patients who received oral pharmacologic therapy than those who underwent neurolytic block. Regarding the third randomized controlled study, the results of Wong and collaborators[105] are welcome in light of a lack of properly designed comparative studies between neurolytic techniques and comprehensive medical management (CMM). However, several issues in the design and results of this study need to be highlighted:

- Patients enrolled in the study did not have severe pain at study entry. Mean pain scores at baseline were 4.4 ± 1.7 in the NCPB group and 4.1 ± 1.8 in the CMM group. This is a surprising finding in patients with this type of malignancy and may reflect ethnic and racial differences in pain perception and reporting by the population enrolled in the study.
- Although the authors reported a significant statistical reduction in pain scores one week after therapy when comparing the NCPB group with the CMM group, the difference between the two groups may not be clinically important. Patients assigned to the NCPB group reported mean pain scores of 2.1 ± 1.4, whereas those randomized to the CMM group reported pain scores of 2.7 ± 2.1 at that time interval. Moreover, statistical difference was found only when the percent reduction from baseline in the NCPB and the CMM group was analyzed separately (53% reduction from baseline in the NCPB group, $P = 0.05$, versus a 27% reduction observed in the CMM group, $P = 0.01$).
- It is critically important to note that most patients (93%) took opiates during the first week of therapy, with similar amounts of opiates being administered to the two treatment groups. Opiate consumption increased with time with no differences between groups at the different time intervals during the study. The incidence of side effects was not different between the two treatment groups at any point in time.
- Likewise, quality of life measurements and the physical and functional wellbeing subscales of the Functional Assessment of Cancer Therapy for Prostate Cancer did not differ between the two groups at any evaluation point.

Two important questions stem from these results:

- Can the authors truly conclude that the major finding of the study was that NCPB significantly improves relief of pain in patients with advanced pancreatic cancer compared to those who received optimized CMM?
- Based on these results, are we justified to submit a patient with advanced pancreatic cancer to NCPB, given the potential side effects and complications associated with this procedure?

We do not believe that the authors can conclude that NCPB significantly improves pain relief in patients with advanced pancreatic cancer. This is partly because the levels of analgesia achieved by the patients assigned to either group after one week of therapy can be considered clinically acceptable. Additionally, statistical difference was found only when the authors analyzed the percent reduction in pain from baseline in each of the treatment groups.

Likewise, based on these results, we do not believe that we would recommend NCPB to a patient with advanced pancreatic cancer because in this not so perfect world, complications do occur, as has been addressed earlier.

Given these reservations, does this mean that we should not perform NCPB in patients with pancreatic malignancy? As with every clinical study, the results of Wong and associates apply only to the population studied and under the conditions of the study protocol design. The critical issue is that *all* patients had nonresectable disease, which suggests that the patients were likely to have other pain components such as somatic or neuropathic, which are not responsive to NCPB.[86] This is because neurolytic blocks of the sympathetic axis are effective in treating visceral pain only. Moreover, previous studies have suggested that in patients with evidence of disease outside the pancreas, such as celiac or portal adenopathy, the success rate of this block decreases significantly.[106] In the study by De Cicco and collaborators, long-lasting

pain relief was described in nine of nine patients (95% confidence interval of 60–100) when contrast medium spread into the four quadrants and in 10–21 patients (95% confidence interval of 26–70) when contrast medium spread into three quadrants. None of the 75 patients with spread of contrast agent into two or one quadrants experienced long-lasting pain relief.[106] Thus the presence of adenopathy secondary to metastasis is a poor prognostic factor for the success of the block. This decrease in effectiveness is not because of a mechanical factor such as big lymph nodes blocking the spread of the neurolytic agent. Rather, it is simply a marker of more extensive disease that often includes nonvisceral pain components and is, therefore, less amenable to NCPB. The results of the study by Wong and collaborators further support the notion that NCPB should not be performed in patients with advanced unresectable carcinoma of the pancreas. This block should be reserved for patients without evidence of disease outside the viscera so that one is guaranteed that the patient has a visceral pain component only.

A prospective, nonrandomized study[107] compared 41 patients treated according to the World Health Organization guidelines for relief of cancer pain with 21 patients treated by NCPB. The authors concluded that this technique could play an important role in managing pancreatic cancer pain.

Since one of the three randomized, controlled studies compared different approaches to the celiac plexus and had no control group,[86] and the other study compared the procedure with an analgesic drug,[104] it is not possible to estimate the success rate of this technique. In contrast, the results of a meta-analysis that evaluated the findings of 21 *retrospective* studies with a total of 1145 patients concluded that adequate to excellent pain relief can be achieved in 89% of patients during the first two weeks following the block.[108] Partial to complete pain relief continued in approximately 90% of the patients who were alive at the three-month interval and in 70%–90% of patients during the three-month interval before death. Its efficacy was similar in patients with pancreatic cancer as in those with other upper intra-abdominal malignancies. However, these results are based on *retrospective* evaluation, which may not yield reliable information or be subject to publication bias. In addition, the statistical techniques used for the analysis must account for the heterogeneity produced by patient selection criteria, technical differences in performance of the blocks, choice of neurolytic agents and doses used, diversity in the tools for evaluation of pain, goals of therapy, and other factors. Thus the meta-analysis must be interpreted with caution because the report may be overly enthusiastic.

Oral pharmacologic therapy with opioids, NSAIDs, and co-adjuvants is used frequently for the treatment of cancer pain. However, the evidence suggests that chronic use of high doses of opioids has a negative effect on immunity.[109] Thus analgesic techniques that lower opioid consumption may have a positive effect on patient outcomes. Lillemoe and colleagues[110] showed in a prospective, randomized trial that patients with nonresectable cancer of the pancreas who underwent splanchnic neurolysis lived longer than those who did not undergo neurolysis. These findings may result from lower opioid use in the neurolysis patients, who had better-preserved immune function and experienced fewer side effects (e.g. nausea and vomiting), thus allowing them to eat better. Although the study by Wong and colleagues[105] did not show that patients randomized to the neurolytic arm of the study lived longer, this may be explained by their high intake of opioids during the study period, which negated the effect of the blocks. The effects of this procedure on long-term survival will need further experimental investigation.

Superior Hypogastric Plexus Block

A variety of visceral and somatic causes can lead to pelvic pain. Such conditions may include endometriosis, inflammatory disease, postoperative adhesions, and cancer. Frequently, the pain is diffuse and vague, a condition called visceral pain and may be interrupted with a targeted sympathetic blockade. Cancer patients with extension of tumor into the pelvis may experience severe pain that is unresponsive to oral or parenteral opioids. In addition, excessive sedation or other side effects may limit the acceptability and usefulness of oral opioid therapy. Therefore a more invasive approach is needed to control pain and improve the quality of life of these patients.

Pelvic pain associated with cancer and chronic nonmalignant conditions may be alleviated by blocking the superior hypogastric plexus.[111–114] Analgesia of the organs in the pelvis is possible because the afferent fibers innervating these structures travel in the sympathetic nerves, trunks, ganglia, and rami. Thus sympathectomy for visceral pain is analogous to peripheral neurectomy or dorsal rhizotomy for somatic pain. One study[114] has suggested that visceral pain is an important component of the cancer pain syndrome experienced by patients with cancer of the pelvis, even in advanced stages. Thus percutaneous neurolytic blocks of the superior hypogastric plexus should be considered more often for patients with advanced stages of pelvic cancer.

A Japanese study group investigated 35 patients with abdominal or pelvic pain (or both) with a large visceral component. They performed three blocks at one time on all the patients: celiac plexus, inferior mesenteric, and superior hypogastric. They reported a 100% immediate success rate, with all patients' VAS pain scores dropping to zero. The statistically significant decrease in pain scores following the procedures persisted for three months. They also found a significant decrease in opiate use following the intervention that persisted for the first month.[112] This again underscores the need for selecting patients with visceral pain for neurolysis.

Clinically Relevant Anatomy

The superior hypogastric plexus (SHP) is situated in the retroperitoneum; it extends bilaterally from the lower third of the fifth lumbar vertebral body to the upper third of the first sacral vertebral body (Fig. 63.2). The plexus lies anteromedial to the psoas muscle and caudal to the bifurcation of the iliac vessel. The SHP sends out multiple branches to various smaller plexuses supplying sympathetic innervation to all the pelvic viscera except the ovaries and fallopian tubes. It extends distally as the hypogastric nerves, which form the inferior hypogastric plexus.

Available Techniques and Approaches

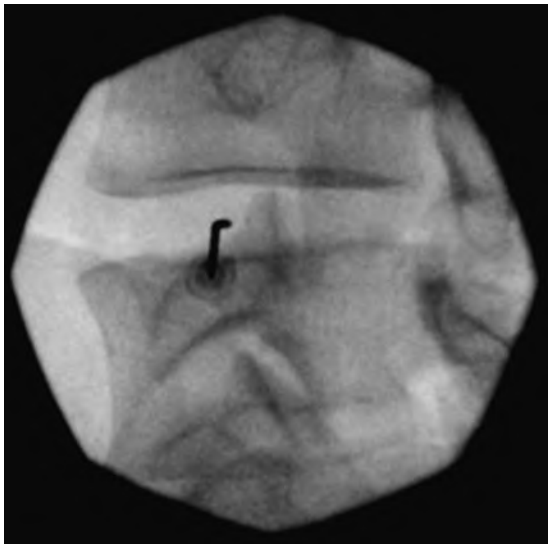
The technique for the blockade has been described elsewhere.[111,114,115] The patient is placed in the prone position with a pillow under the pelvis to flatten the lumbar lordosis. Two 7-cm needles are inserted with the bevel directed 45 degrees medially and 30 degrees caudad so the tips lay anterolateral to the L5-S1 intervertebral disk space. Aspiration is important to avoid injection into the iliac vessels. If blood is aspirated, a transvascular approach can be used (see the section "Complications"). Accurate placement of the needle is verified by biplanar fluoroscopy. Anteroposterior (AP) views should reveal the tip of the needle to be at the level of the junction of the L5 and S1 vertebral bodies. This is an important safety step to avoid the potential spread of

the neurolytic agent toward the L5 roots (see "Complications"). Lateral views will confirm the placement of the needle's tip just beyond the vertebral body's anterolateral margin. Injection of 3–5 mL of water-soluble contrast medium is used to verify accurate needle placement and rule out intravascular injection. In the AP view, the spread of contrast material should be confined to the midline region. In the lateral view, a smooth posterior contour corresponding to the anterior psoas fascia indicates that the needle is at the appropriate depth. For a prognostic hypogastric plexus block or patients with non-cancer related pain, local anesthetic alone is used. For therapeutic purposes in patients with cancer related pain, phenol is typically used as the neurolytic solution.

Mastering this technique is difficult because the transverse process of L5 makes it difficult to access the anterior portion of the L5-S1 region. Consequently, a transdiscal approach has been suggested (Figs. 63.22–63.24). However, this approach may be associated with the inherent risk of puncturing the intervertebral disk.[113]

More recently, an ultrasound guided anterior approach was described that permits visualization of the iliac vessels and vertebral body.[116] It may be prudent to confirm the spread of contrast dye with fluoroscopy, especially before the instillation of neurolytic solutions, when the needle was placed under ultrasound guidance.

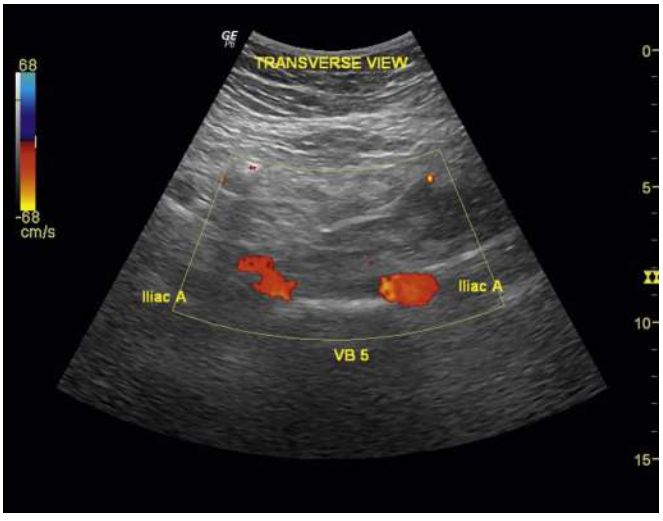
With a curved-array transducer and the patient supine, the aorta is traced caudally until it bifurcates into the iliac arteries (Fig. 63.25). The use of color Doppler facilitates proper identification. Medial and posterior to the bifurcation, the fifth lumbar vertebral body may be visualized. The target is over the anterior and most caudal portion of the fifth lumbar vertebral body. The planning of the trajectory is based on the location of the vessels (Fig. 63.26). The area over the possible needle entry point is prepared and draped. Using sterile technique, a 22-gauge spinal needle is advanced either out of plane or in plane to the anterolateral border of the vertebral body. Following placement, it may be



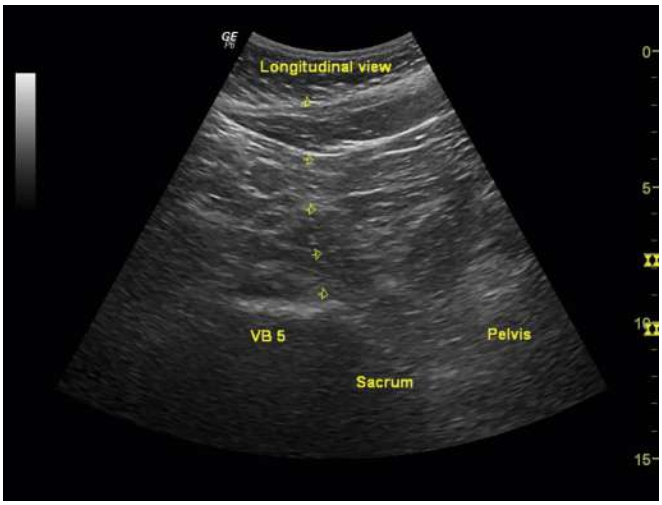
• **Figure 63.22** Transdiscal positioning of the needle at L5-S1 for a superior hypogastric plexus block on an oblique view.

• **Figure 63.24** Transdiscal positioning of the needle at L5-S1 for a superior hypogastric plexus block on an anteroposterior view.

• **Figure 63.23** Transdiscal positioning of the needle at L5-S1 for a superior hypogastric plexus block on a lateral view.



• **Figure 63.25** Transverse sonographic view in Doppler mode showing the bifurcation of the aorta into the iliac vessels.



• **Figure 63.26** Transverse sonographic view showing the fifth lumbar vertebral body. The *line* marks the trajectory for the needle.

prudent to confirm accuracy with digital subtraction angiography before injection of local anesthetic. The typical volume used is approximately 10 mL on each side. Neurolytic agents may be used after confirmation of pain relief with local anesthetic. Administration of antibiotics beforehand is recommended.

Indications

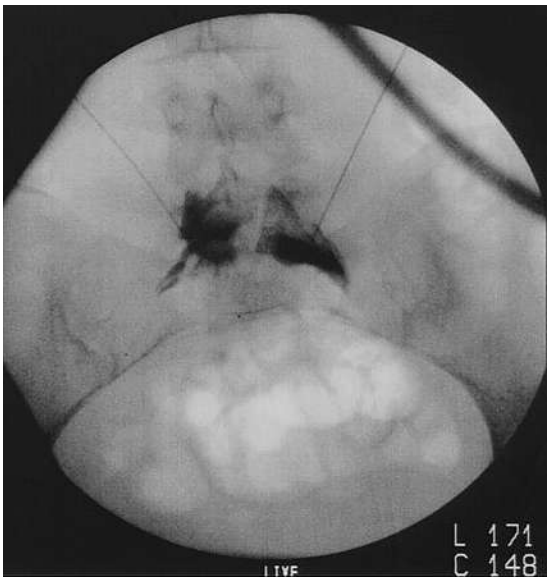
Blockade of the SHP provides relief of pain originating from pelvic viscera secondary to various types of cancer and endometriosis. Superior Hypogastic Plexus Block (SHPB) has also been reported to provide relief from postprostatectomy penile pain, urethral pain, and post-uterine artery embolization pain.[117-120]

Complications

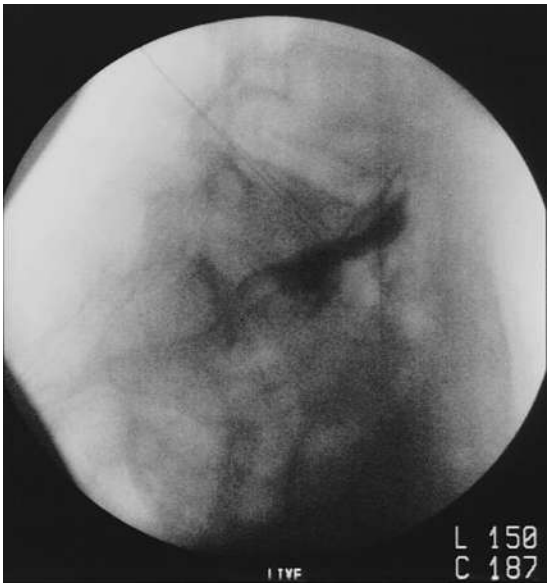
The combined experience of over 200 cases from the Mexican Institute of Cancer, Roswell Park Cancer Institute, and M.D. Anderson Cancer Center indicates that neurologic complications have not occurred as a result of this block.[115] However, extreme care should be exercised because placing the tip of the needle in the upper middle portion of L5 may be associated with retrograde spread to the nerve roots. If such spread is not recognized, injection of the neurolytic agent could result in predictable neurologic deficits (Figs. 63.27 and 63.28).

Efficacy

The effectiveness of the superior hypogastric plexus block was originally demonstrated by a significant decrease in pain via VAS pain scores. In their study, Plancarte and colleagues[111] showed that the block was effective in reducing VAS pain scores in 70% of patients with pelvic pain associated with cancer. The majority of the patients enrolled had cervical cancer. In a subsequent study,[114] 69% of the patients experienced a decrease in VAS pain scores. A mean daily reduction in opioid use of 67% was seen in the success group (736 ± 633 reduced to 251 ± 191 mg/d) and 45% in the failure group (1443 ± 703 reduced to 800 ± 345 mg/d).[114] In a later multicenter study,[115] 159 patients with pelvic pain associated with cancer were evaluated. Overall, 115 patients (72%) had satisfactory pain relief after one or two neurolytic procedures. Mean opioid use decreased by 40% from 58 ± 43 to 35 ± 18 mg/d of morphine equivalents three weeks after treatment in all the patients studied. This decrease in opioid consumption was significant in both the success group



• **Figure. 63.27** Improper needle placement for intended superior hypogastric neurolysis. Note the spread of contrast medium to the L5 nerve root.



• **Figure 63.28** Lateral view of the same patient as in Fig. 63.27.

(56 ± 32 reduced to 32 ± 16 mg/d) and the failure group (65 ± 28 reduced to 48 ± 21 mg/d).[115] Success was defined in the two studies as the ability to reduce opioid consumption by at least 50% in the three weeks following the block and a decrease in VAS pain scores to below four of ten.[103,114]

In a case report, Rosenberg and colleagues[121] reported on the efficacy of superior hypogastric plexus block in a patient with severe chronic nonmalignant penile pain after transurethral resection of the prostate. Although the patient did not receive a neurolytic agent, a diagnostic block performed with 0.25% bupivacaine and 20 mg methylprednisolone acetate was effective in relieving the pain for more than six months. The usefulness of this block for chronic benign pain conditions has not been adequately documented.

Thus SHPB may be performed for the relief of pelvic pain under imaging guidance through either an anterior or posterior approach. The major advantage of an anterior approach is patient comfort. Although CT and fluoroscopy guided approaches have been described, they have the disadvantage of excessive radiation exposure. An ultrasound guided anterior approach may be used for needle placement with subsequent fluoroscopic contrast confirmation. The safety, reproducibility, and efficacy of this technique still need to be established.

Ganglion Impar Block

The ganglion impar is a solitary retroperitoneal structure located at the level of the sacrococcygeal junction. This unpaired ganglion marks the end of the two sympathetic chains. Visceral pain in the perineal area associated with malignancy may be treated effectively by neurolysis of the ganglion impar (Walther's).[122] Patients who will benefit from this block frequently have vague, poorly localized pain that is frequently accompanied by sensations of burning and urgency. However, the clinical value of this block is not clear because the published experience is limited.

Clinically Relevant Anatomy

The ganglion impar is an irregularly shaped terminal ganglion of the sympathetic chain that is usually located close to the midline. The variably shaped ganglion is approximately 4 mm long. It may be located anywhere from the anterior surface of the sacrococcygeal junction to the lower coccygeal vertebral bodies. The exact location follows a gaussian distribution centered on the first to second coccygeal vertebrae.[123] The ganglion impar has gray nerve fiber communication from the ganglion to the spinal nerve but appears to lack white nerve fibers, which communicate pulses from the spinal nerves to the ganglion in the thoracic and upper lumbar regions.[122] Visceral afferents innervating the perineum, distal part of the rectum, anus, distal end of the urethra, vulva, and distal third of vagina converge at the ganglion impar.

Indications

GIB is indicated for sympathetically mediated pain in the region of the anus, distal part of the rectum, urethra, and vagina. Coccygodynia following trauma, infection, degenerative changes, and subluxation has also been relieved temporarily with this block.[124-132]

Available Techniques and Approaches

The original technique was described by Plancarte and collaborators.[122] The technique calls for the patient to be placed in the lateral decubitus position with the hips fully flexed. A standard 22-gauge, 3.5 inch spinal needle is bent 1 inch from its hub to form a 30 degree angle. The needle is then introduced under local anesthesia through the anococcygeal ligament with its concavity oriented posteriorly. Under fluoroscopic guidance, it is directed along the midline at or near the sacrococcygeal junction while placing a finger in the rectum to avoid puncturing this structure. Retroperitoneal location is verified by observation of the spread of 2 mL of water-soluble contrast medium. An alternative needle geometry, in which the needle is bent to the shape of an arc, has been proposed by Nebab and Florence.[133]

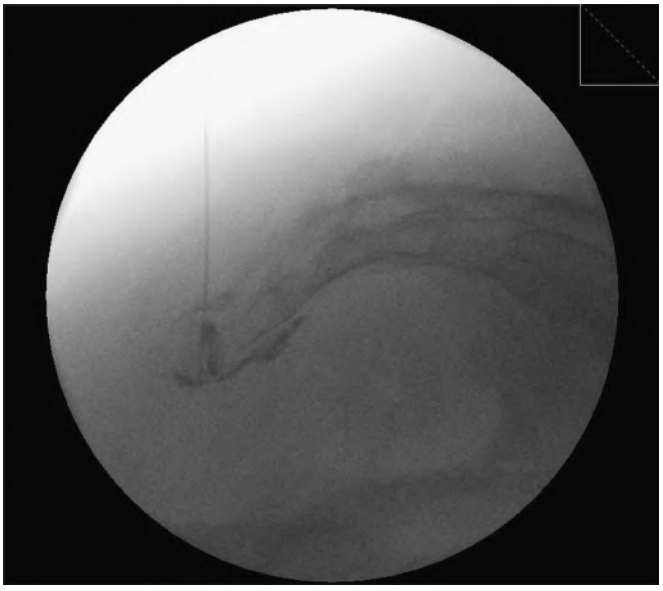
An easier technique is the trans-sacrococcygeal approach (Fig. 63.29),[134] in which the tip of the needle is placed directly into the retroperitoneal space by inserting a 20-gauge, 1.5 inch needle through the sacrococcygeal ligament under fluoroscopic guidance so that the tip of the needle is just anterior to the anterior portion of the sacrum. This technique avoids invasion of more caudal structures (rectum) by the needle and the need to insert a finger in the rectal lumen.

For diagnostic blocks, local anesthetic alone is used. For neurolytic blocks, 6% phenol is recommended. Cryoablation of the ganglion impar has also been described for repeated procedures via a trans-sacrococcygeal approach in a patient with chronic benign pain after abdominoperineal resection.[135]

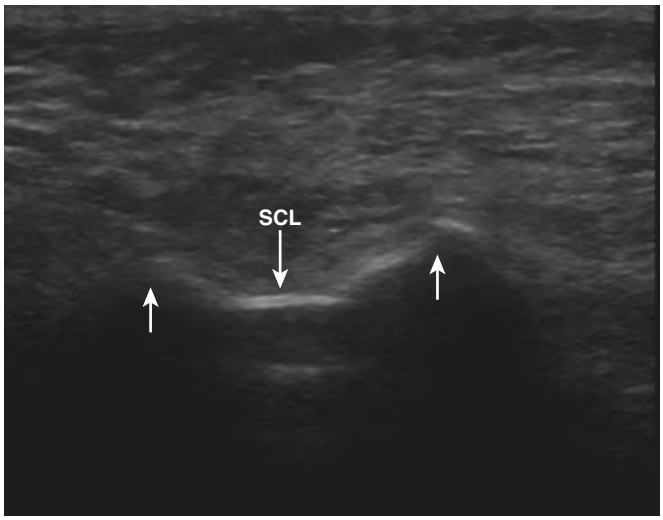
Technique of Ultrasound Guided Ganglion Impar Block

The patient is positioned prone with a pillow underneath the pelvis, and the hips externally rotated to provide exposure of the perineum. The skin is prepared with a suitable antiseptic solution and draped in a sterile manner. A preliminary scout scan is performed in the transverse and longitudinal views with a linear-array transducer in a sterile sleeve to visualize the sacrum and coccyx. The coccyx is then brought to the middle of the field in a longitudinal view, and a suitable trajectory is planned (Figs. 63.29 and 63.31). While keeping the coccyx in the longitudinal view, a skin wheal is raised with 1% lidocaine at the point of needle entry just caudal to the transducer. A Quincke-type spinal needle is then directed from the caudad to the anterior part of the first coccygeal vertebral body via an in plane technique with real-time visualization of the needle (Fig. 63.32). The tip of the needle may not be visualized clearly beneath the coccyx because of the acoustic shadow. Alternative methods are to use an out of plane technique for the trans-sacrococcygeal or paracoccygeal approaches. This provides a smaller trajectory, but needle visualization is poorer.

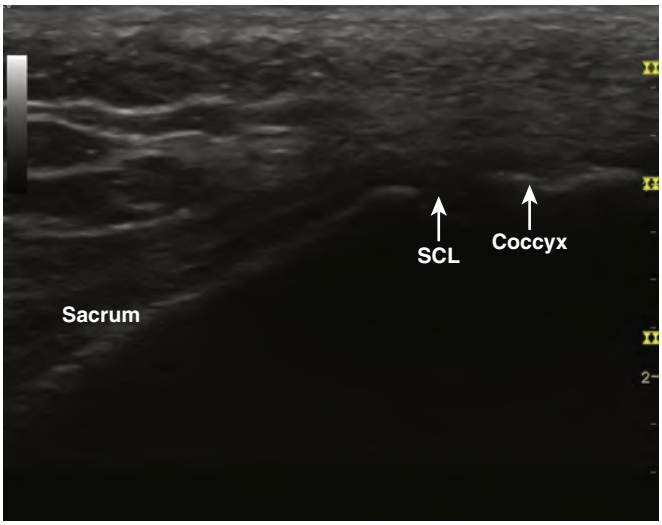
Further confirmation is provided by a lateral fluoroscopic view, which should show the needle to be suitably positioned just anterior to the coccyx and posterior to the rectum. Under fluoroscopic guidance, 0.5–1 mL of contrast agent is injected to confirm the proper spread of the dye, which appears as a "comma sign," before injecting a local anesthetic, steroid, or neurolytic substance (Fig. 63.29). Injection of a local anesthetic to confirm pain reduction before steroid injection or neurolytic intervention may be recommended. The total volume required is usually about 2–4 mL.



• **Figure 63.29** Fluoroscopic transverse image of the sacrum and coccyx with the needle in a transcoccygeal approach showing the spread of contrast dye along the anterior surface of the coccyx.



• **Figure 63.30** Transverse sonographic view of the sacral hiatus. The arrows point to the cornu of the sacral hiatus. *SCL*, Sacrococcygeal ligament.



• **Figure 63.31** Longitudinal sonographic view of the sacrum, coccyx, and needle *(arrows)* placed in an in plane approach through the anococcygeal ligament.

Efficacy

Three studies evaluated the efficacy of ganglion impar blocks in a prospective, nonrandomized, noncontrolled fashion. Plancarte and colleagues[122] evaluated 16 patients with advanced cancer (cervix, nine; colon, two; bladder, two; rectum, one; endometrium, two) and persistent pain despite treatment (pharmacologic management resulted in a 30% global reduction in pain). Localized perineal pain was present in all cases and was characterized as burning and urgent in eight patients and of mixed character in the other eight. Pain was referred to the rectum (seven patients), perineum (six patients), or vagina (three patients). Eight patients reported complete pain relief after a neurolytic block via a transanococcygeal approach, whereas the remainder experienced a significant reduction in pain (60%–90%). Blocks were repeated in two patients, and follow up was conducted for 14–120 days, depending on survival.

Swofford and Ratzman[136] reported on the efficacy of the transsacrococcygeal approach. Twenty patients with perineal pain unresponsive to the previous intervention were studied, 18 with a bupivacaine/steroid block and two with a neurolytic block. In the bupivacaine/steroid group, five patients reported complete (100%) pain relief, 10 reported a greater than 75% reduction in pain, and three reported a greater than 50% reduction in pain. Neurolytic blocks resulted in complete pain relief. Duration of the pain relief varied from four weeks to long-term.

Vranken and colleagues[137] studied the effect of a ganglion impar block for long-lasting, treatment-resistant coccydynia. Twenty patients, including 17 females and three males, diagnosed with coccydynia (spontaneous, seven; fracture, three; injury, 10) received a 5 mL injection of 0.25% bupivacaine. There was no reduction in pain or increase in quality of life associated with the procedure. Thus based on this study, it would appear that this block is not effective for the treatment of coccydynia.

Complications

Although there is always a risk of damaging structures adjacent to the ganglion impar, no complications have been reported with this technique. Plancarte and coauthors[138] reported one case in which epidural spread of contrast medium within the caudal canal was observed. In this case, repositioning the needle resolved the problem. Although published experience is limited and criteria for predicting success or failure are not available, patients with poorly localized perineal pain with a burning character are considered candidates for a ganglion impar block. The procedure is safe, and no complications have been reported.

Conclusion

Neurolysis of the celiac plexus/splanchnic nerves, superior hypogastric plexus, or ganglion impar may be used in patients with visceral pain of the upper part of the abdomen, pelvis, and perineal region, respectively. Use of this technique in patients who do not have a significant visceral pain component is not warranted. The presence of disease in the corresponding lymph nodes is a poor prognostic marker for these blocks. The incidence of reported complications is low. However, they may occur and have significant implications on the quality of life of the patient. Thus strict adherence to the technique is important to prevent potential problems.

Key Points

- Chemical neurolytic therapy should only be considered after other pain modalities have been exhausted. These therapies are usually reserved for patients with a terminal disease. Very clear therapeutic goals and limitations need to be communicated between patient and practitioner.
- Chemical neurolytics can offer patients the ability to decrease their systemic pain medications that can improve their quality of life and allow them the opportunity to communicate with loved ones during difficult times.
- Alcohol and phenol are the primary agents used in intrathecal and epidural chemical neurolysis. Alcohol is associated with burning upon injection, so it is preceded by local anesthetic injection. Phenol injection is relatively painless and is associated with a feeling of warmth. Glycerol is used or trigeminal neurolysis.

- Pain location should be pinpointed with sclerotome, dermatome mapping, and radiologic survey. For neuraxial injections, the patient's positioning for injection is determined by patient comfort and by which agent is to be injected. Alcohol is hypobaric and "floats" in CSF, whereas phenol is hyperbaric and "sinks" in CSF.
- The most common complication is poor pain relief. Often, pain relief may require several injections. Other complications related to intrathecal or epidural neurolytics are loss of motor function, loss of touch or proprioception, and loss of bowel or bladder sphincter tone.
- Neurolytic blocks of the sympathetic axis are used for the control of chronic upper abdominal and pelvic pain in patients with cancer.
- A study has shown that even in the best-case scenario, the duration of full pain control with a neurolytic block is two months.
- The goals of a neurolytic block are to maximize the analgesic effect of pharmacotherapy and reduce the dosage of these agents to alleviate side effects.
- A *stellate ganglion block* has historically been used to treat numerous pain related and unrelated conditions. Evidence of its efficacy is limited. Blind injections are inaccurate and risky. Ultrasound guidance is the preferred method to ensure accuracy and safety.
- The *celiac plexus* is situated retroperitoneally in the upper part of the abdomen at the level of the T12 and L1 vertebrae, anterior to the crura of the diaphragm. The celiac plexus is supplied by the greater, lesser, and least splanchnic nerves originating from T5 to T12.
- Three approaches to block the celiac plexus include the retrocrural (or classic) approach, the anterocrural approach, and neurolysis of the splanchnic nerves.
- An analgesic or NCPB is less effective in managing nonmalignant abdominal pain.
- Pelvic pain associated with cancer and chronic nonmalignant conditions may be alleviated by blocking the *superior hypogastric plexus*.
- A *ganglion impar block* provides relief of coccygodynia and pain involving the lower part of the rectum, anus, urethra, and vagina.
- Visceral pain in the perineal area associated with malignancy may be treated effectively by neurolysis of the *ganglion impar*.

Suggested Readings

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64

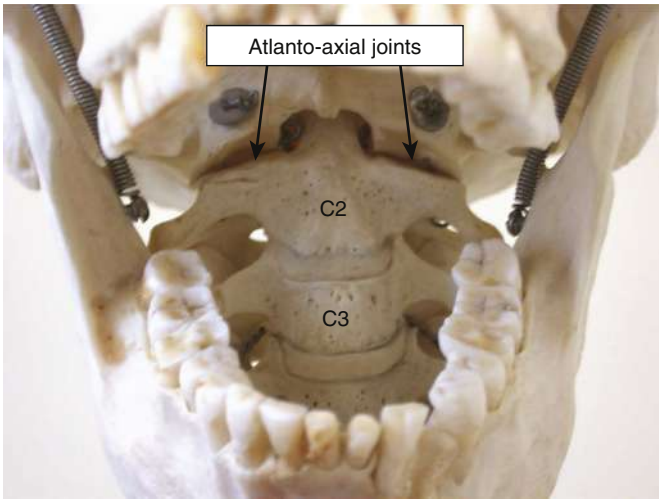
Head and Neck Blocks

ANTOUN NADER, JEE YOUN MOON, MARY LEEMPUTTE, KENNETH D. CANDIDO

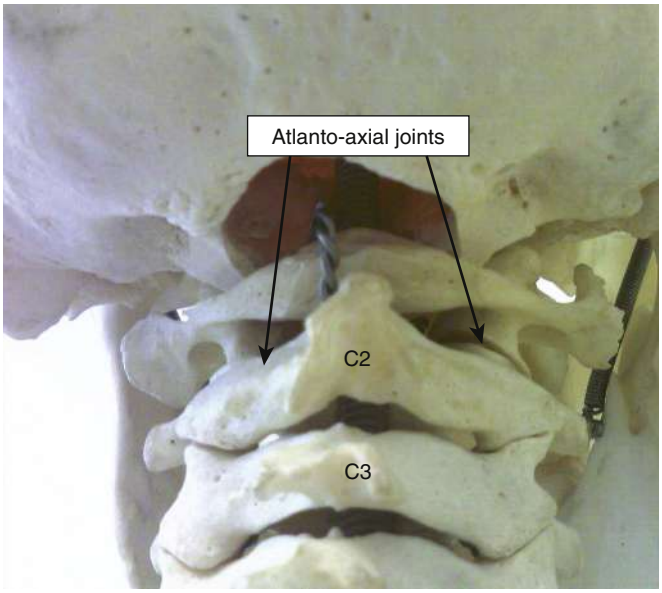
Head and neck blocks consist of blockade of the atlanto-axial joint, third occipital nerve, occipital nerve, sphenopalatine ganglion, trigeminal nerve, and glossopharyngeal nerve. This chapter will discuss the rationale for these blocks, the relevant anatomy, and the technique in performing the blocks. There has been tremendous progress in the performance of these blocks, mirroring the progress of other peripheral nerve blocks: from landmark technique to use of fluoroscopy and, recently, ultrasound. Discussion on the efficacy of many of these blocks is not complete, reflecting the state of published studies.

Atlanto-Axial Joint Blockade

The primary indication for performing an atlanto-axial (A-A) nerve block is for the diagnostic and therapeutic evaluation of suboccipital pain that occasionally radiates into the temporomandibular joint area that is exacerbated by head rotation. Whiplash injuries and cervicogenic headaches are two of the more common indications for this block. The A-A joint (Figs. 64.1 and 64.2, previously Figs. 52.1 and 52.2) lacks posterior articulations and therefore is neither a bona fide facet joint nor a true zygapophyseal joint. Furthermore, there is no intervertebral disc between the atlas (C1) and the axis (C2), nor is there an intervertebral foramen at that level to accommodate an exiting nerve root. At the A-A joint, the head flexes, extends, and rotates in a horizontal plane, up to 60 degrees, giving the joint significant responsibility for both the stability and the mobility of the head and neck. The joint can be injured by seemingly trivial insults and trauma. The resulting pain syndrome can be significant, manifesting as dull, continuous, and achy pain in the posterior neck and suboccipital region. More severe injuries, such as those caused by motor vehicle accidents, might subject the joint to acceleration-deceleration type injuries, with sequelae exceeding pain and dysfunction. Indeed, paralysis and even death could result from ligamentous disruption, analogous to an odontoid fracture. The fibers of the respective spinal nerves C1 and particularly C2 contribute to the formation of the occipital nerves (greater and lesser), which are a frequent target for the practicing pain physician in contemporary practice. An extremely important anatomic concept involves the relationship of the vertebral artery to the A-A joint; whereas the artery is medial to the atlanto-occipital (A-O) joint,[1] it is found lateral to the A-A joint. Therefore needles directed at the joint during nerve block need to be oriented slightly more medially, cognizant of the danger of aiming toward the interlaminar space or even toward the foramen magnum.



• **Figure 64.1** Demonstration of the mouth open view to reveal the anterior atlanto-axial (C1-C2) joint. (Photo courtesy of Kenneth D. Candido, M.D.)

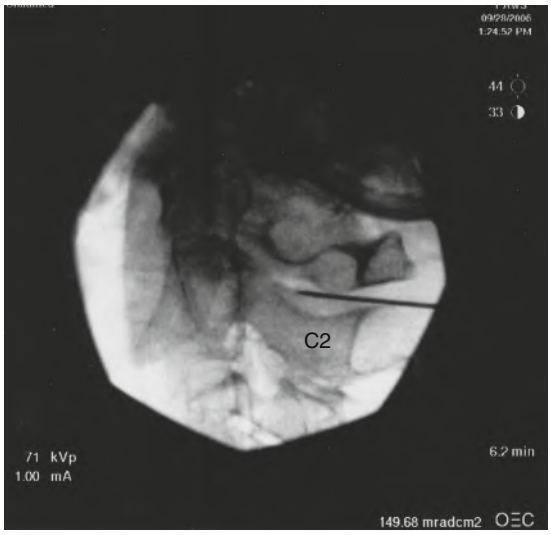


• **Figure 64.2** Posterior view of the atlanto-axial (C1-C2) joint. (Photo courtesy of Kenneth D. Candido, M.D.)

Technique of Atlanto-Axial Nerve Blockade (Figs. 64.3 and 64.4, previously Figs. 52.3 and 52.4)

Blockade of the A-A joint requires fluoroscopic assistance to ascertain that the advancing needle does not encroach upon the critical anatomical structures such as the vertebral artery and the spinal cord. Appropriate medical history is obtained, and a targeted physical examination is performed. After establishing no bleeding problems or infectious issues and baseline vital signs taken and recorded, the patient is placed prone. Baseline vital signs are obtained and recorded. It is recommended that an intravenous peripheral line be established for prophylactic purposes. Bolsters are typically placed beneath the chest to elevate the shoulders off the procedure table, permitting the patient to flex the neck and rest the forehead upon a neurosurgical donut or pillow. After performing a careful sterile skin preparation and draping, the fluoroscopic unit is oriented in an anterior-posterior direction to identify the atlas and the foramen magnum, implementing a moderate cranial tilt of the unit until all structures are clearly visualized. The A-A joint is located lateral and inferior to both the foramen magnum and the atlas (Fig. 64.2). After a local anesthetic skin wheal, an 18-gauge skin core is made using a sharp cutting needle to permit the passage of a blunt, 22-gauge, styletted Whitacre type subarachnoid needle. (A curve placed at its distal tip to allow steering of the needle once it has been advanced through the skin and subcutaneous tissues.) The needle is advanced under continuous fluoroscopic guidance, rotating the beam of the unit until the needle appears in a tunnel or "gun barrel" view, which is represented as a dot advancing toward the posterolateral aspect of the A-A joint. The needle should be directed slightly medially to avoid the vertebral artery, which is situated laterally, but not too medially, as this would potentially engage the spinal cord. Occasionally, but not always, a "popping" sensation will be appreciated as the needle traverses the joint and enters it from posterior to anterior (Fig. 64.3). The fluoroscopic unit must then be rotated laterally (Fig. 64.4) to confirm the needle placement at the appropriate depth between the atlas and axis. Once placement has been verified, gentle aspiration of the needle is undertaken to assess for the presence of cerebrospinal fluid (CSF) or blood. If CSF or blood is not present, a small (i.e. 1 mL) volume of radiocontrast media may be incrementally injected under real-time fluoroscopy. If the needle is indeed situated within the confines of the joint, a bilateral concavity will be demonstrated, which is indicative of an intact joint capsule. However, if the joint capsule has been ruptured, the dye may be seen to spread into the peridural space. Long acting local anesthetics (bupivacaine, ropivacaine) should not be injected. Rapid runoff of the dye may signify vascular injection and is to be guarded against, particularly if it is suspected that the needle may have entered the laterally situated vertebral artery. If this occurs, the needle should be redirected medially, re-aspiration of the needle in four quadrants undertaken, and re-injection of contrast material prior to considering injecting local anesthetics or adjuvants. Even without directly injecting into the vertebral artery (even minuscule volumes of dilute local anesthetics injected here can lead to grand mal seizures), ataxia following A-A block is not uncommon and is likely because of vascular uptake of local anesthetics in this extremely vascular region.[2]

• **Figure 64.3** Posterior-anterior radiograph demonstrating correct needle placement using a posterior approach to the left atlanto-axial joint. (Photo courtesy of Kenneth D. Candido, M.D.)

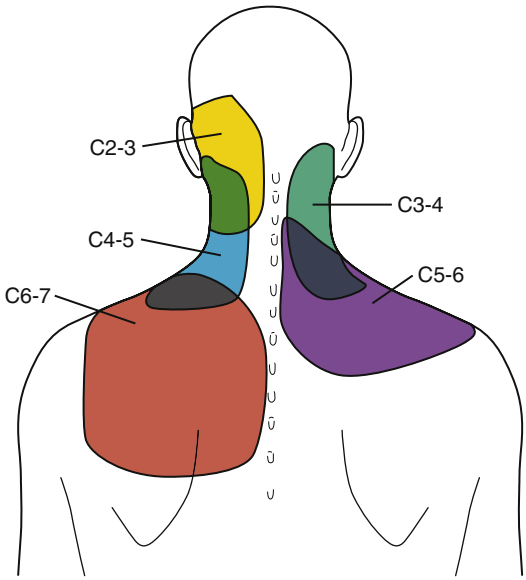


• **Figure 64.4** Lateral fluoroscopy demonstrating appropriate needle placement for an atlanto-axial joint injection. (Photo courtesy of Kenneth D. Candido, M.D.)

Third Occipital Nerve Blockade

Diverse pain syndromes result from disorders of the cervical intervertebral discs, the facet joints (zygapophyseal, or Z-joints), or both. When confronted by individuals with headache and neck and/or shoulder pain, the clinician is compelled to seek a diagnosis based largely upon history and physical examination. The physical examination is complicated by significant variability and overlap in the innervation patterns related to the sensory distribution of the cervical medial branch nerves (Fig. 64.5, previously Fig. 52.5). The third occipital nerve has been implicated in chronic headache pain, primarily as attributed to cervicogenic headache. There is little doubt that syndromes related to dysfunction of the medial branch nerves of the upper cervical spine have at times been misdiagnosed as being because of tension-type and other forms of headache. Consequently, these patients who have been misdiagnosed have ultimately failed to derive analgesic benefit from medication administration and other conservative treatment measures.

The third occipital nerve (TON) is the superficial branch of the C-3 dorsal ramus. It is the only medial branch nerve that

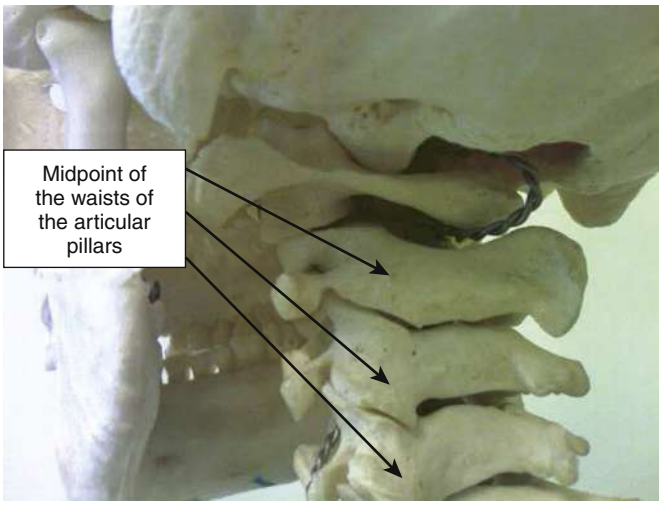


• **Figure 64.5** Map of areas invested by the sensory nerves of the cervical medial branches. (From Cooper G, Bailey B, Bogduk N. Cervical zygapophysial joint pain maps. *Pain Med.* 2007;8:344–353.)

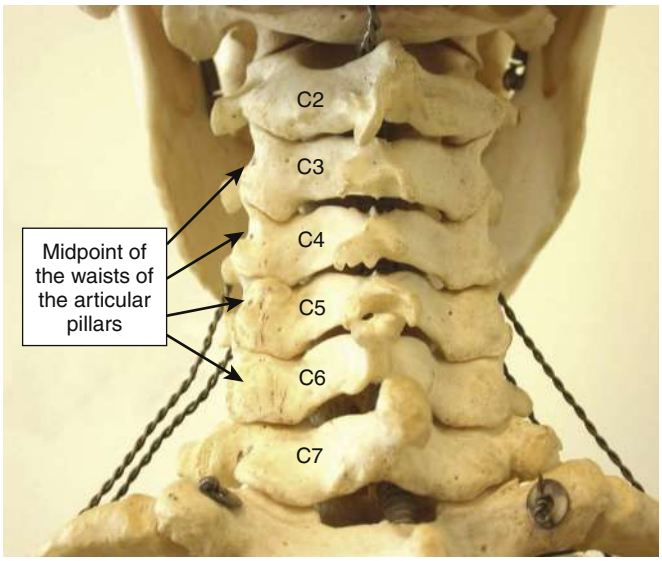
innervates the facet joint at C2–C3 (Figs. 64.6–64.8, previously Figs. 52.6–52.8). Therefore successful blockade of the TON and the resultant block of the facet joint at C2–C3 has been associated with relief of headache pain in individuals suffering from "third occipital headache."

Anatomical Considerations

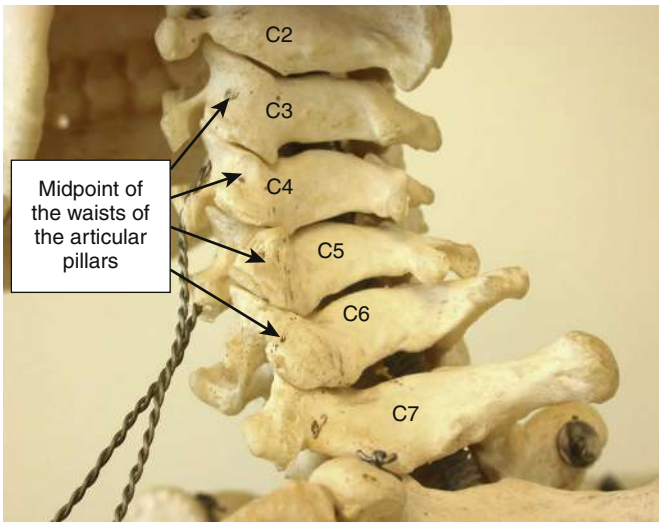
The C2–C3 joint is the first joint of the cervical spine possessing a true joint capsule and synovium, and this is the first level where an intervertebral disc and a foramen exist to accommodate the exiting C3 nerve root. In this regard, the C2–C3 joint is distinct from the atlanto-occipital (AO) (C0–C1) and atlanto-axial (AA) (C1–C2) joints superior to it. This level then represents a sort of transitional zone between the rotational joint of the neck (AA)



• **Figure 64.6** Lateral oblique view demonstrating close-up of the needle insertion points for medial branch blocks and radiofrequency ablation techniques of cervical facet joint denervation. (Photo courtesy of Kenneth D. Candido, M.D.)



• **Figure 64.7** Posterior view of the scalloped areas representing the waists of the cervical articular pillars, the site of needle placement for both local anesthetic medial branch facet joint block, as well as for radiofrequency ablation procedures and pulsed radiofrequency techniques of denervating or neuromodulating the cervical facet joint nerves. The C7-T1 interlaminar opening is more capacious than more proximal levels and is the site frequently chosen for cervical epidural needle placement. (Photo courtesy of Kenneth D. Candido, M.D.)



• **Figure 64.8** Lateral oblique view demonstrating the waists of the articular pillars in consideration of medial branch blocks of the cervical facet joints. Also demonstrated is the interlaminar space at C7–T1 for cervical epidural block needle placement. (Photo courtesy of Kenneth D. Candido, M.D.)

and the lower cervical facet joints, which function not in the neck and head rotation but in neck flexion and extension.

Facet joints contain free and encapsulated nerve endings. In addition, nerves in the zygapophyseal joint (Z-joint) contain substance P and calcitonin gene-related peptide. The capsule of the Z-joint contains low threshold mechanoreceptors, mechanically sensitive nociceptors, and silent nociceptors. Each of these may respond to noxious stimulation, including moderate to severe levels of osteoarthritis, with the result being a nociceptive stimulation perceived as headache or neck pain.

The clinical anatomy of the cervical dorsal rami was described by Bogduk following dissections of five adult cadavers.[2] He pointed out some 30 years ago that classic textbook descriptions of the cervical dorsal rami had been limited in scope and detail. While dissecting the medial branches, he was able to place wires superficially and parallel to the nerves and then perform radiographic analyses of the wires in relation to the cervical vertebral skeleton. It was noted that the semispinalis capitis muscle covers the cervical medial branches, while the lateral branches of C3-C7 lie superficial to the tendons of origin of that muscle. The TON penetrates the semispinalis capitis. The C3 dorsal ramus, a short nerve, was noted to arise from the C3 spinal nerve in the C2-C3 intervertebral foramen and then curve dorsally through the intertransverse space. At this point, the C3 dorsal ramus was noted to divide into three major branches: the two medial branches, the lateral branch, and a communicating branch. In three out of five of his specimens, the two medial branches of C3 were noted to arise from a common stem, and in the other two specimens, they had their own respective origins. The TON was the principal and constant medial branch of the C3 dorsal ramus.[2] After arising from the C3 dorsal ramus, the TON was found to curve dorsally and medially around the superior articular pillar of the C3 vertebral body, crossing the C2-C3 Z-joint either just below the joint itself or at the joint level. The TON runs transversally medially through the fibro-adipose tissue below the obliquus inferior and dorsal to the lamina of the C2 vertebra.

A branch of the TON supplies the semispinalis capitis, which lies superficial to it. A communicating branch to the greater occipital nerve (GON) is also given off. This branch arises just above the level of the C2 spinous process. The TON then passes dorsally and pierces the semispinalis capitis and the splenius capitis, turning rostrally to pierce the trapezius, which lies over it. The more medial terminal branch supplies the skin of the rostral neck and the occiput below the external occipital protuberance. More lateral branches travel toward the mastoid process, communicating with the cutaneous rami of the GON and lesser occipital nerves (LON). Because of the transverse direction of the GON and the TON, these two nerves may be injured by parasagittal incisions made in the upper part of the neck.

The target branch for the nerve block, the TON, wraps dorsally and medially around the middle of the waist of the articular pillar of C3 (center of the bony trapezoid). As it moves more medially, the TON invests the multifidus muscle. There is a communicating branch that typically arises from the C3 dorsal ramus, running rostromedially across the posterior part of the C2–C3 Z-joint.[2] The anatomic target for locating the nerve percutaneously is to utilize lateral fluoroscopy to identify the waistline of the articular pillars of C2 and C3 and to advance a needle or radiofrequency cannula toward the Z-joint at C2–C3. As Bogduk stated, "needles or electrodes introduced obliquely, ventromedially onto the dorsolateral aspect of the articular pillar, will rest on the medial branch. The relationship of the nerve to bone at this site is constant because the medial branches are bound to the periosteum by an investing fascia and are held against the articular pillar by tendons of the semispinalis capitis."[2] This target is both removed from any major arterial (vertebral artery) or other vascular structure, as well as from the exiting spinal nerve and spinal cord and is, therefore, both an appropriate target in terms of affording access to the medial branches, as well as one which provides for an approach likely to minimize unwanted trespass into non-targeted tissues.

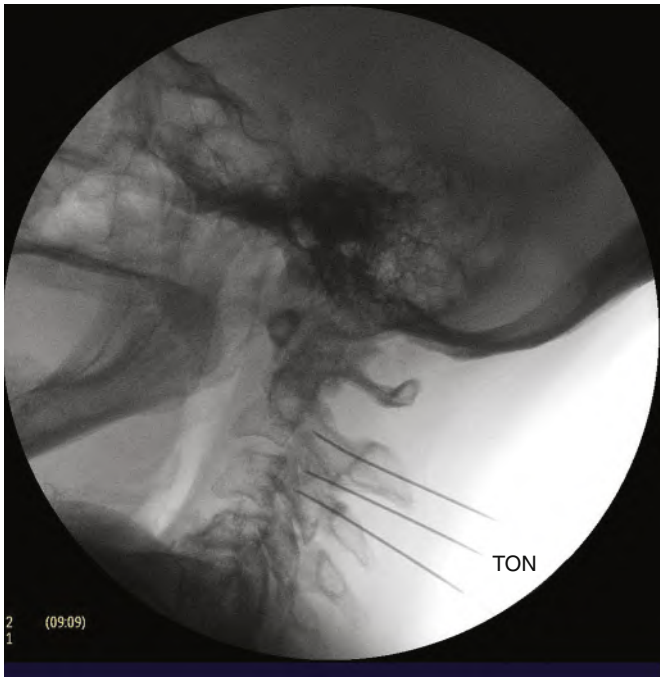
The Third Occipital Nerve and Headache Pain

Osteoarthritis of the C2–C3 Z-joint and trauma related to motor vehicle accidents are causes of persistent occipital or suboccipital headache pain. As there is no clear-cut clinical evaluative technique or diagnostic tool for determining patients who suffer from a headache because of disease of this joint or from neck trauma (or that mediated by the TON), it is somewhat intuitive and logical that blockade of the TON should be performed in cases of persistent headache that are unresponsive to conventional medication management.[3]

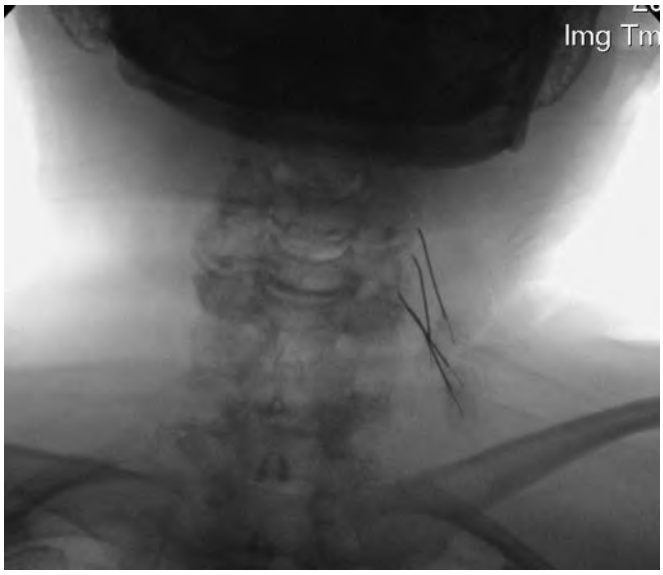
Bogduk and Marsland conducted fluoroscopically guided TON blocks in ten consecutive patients presenting with occipital or suboccipital headache.[3] They elected to place their needles at the lower half of the silhouette of the C2–C3 Z-joint, recognizing the landmark on X-ray as a convexity arising upwards from the concavity of the C3 articular pillar, lying horizontally opposite the level of the C2 spinous process and C2–C3 disc space (Figs. 64.9–64.11). All procedures were performed with patients in the prone position and with a bolster beneath the upper chest and shoulders to permit head flexion forward toward the procedure table. Injected was 0.5 mL of 0.5% bupivacaine into three distinct sites; in the middle of the Z-joint at C2–C3, one injection at the lower end of the joint, and one between the first two needle placements (for bilateral blocks, the total volume was 3 mL; 1.5 mL per side). Seventy percent of patients manifest total pain relief lasting the duration of the bupivacaine following unilateral blocks.[3] The 30% failures did not have positive responses to the bilateral blocks that were performed on their behalf. Bogduk stated that blockade of the medial branch nerves, particularly the TON, is easier for patients to tolerate than intraarticular injections since they are more easily performed and are associated with less pain during their performance than are the articular injections. Furthermore, it is apparent that local anesthetic injected into a joint may not actually stay within the joint space, potentially limiting any diagnostic information that might otherwise be derived from the procedure. Finally, markedly degenerated joints might not readily accommodate an advancing needle tip, rendering the choice of this articular approach potentially useless overall.[2] If the ventral margin of the joint space is penetrated, there is also a distinct possibility that entrance into the epidural or subarachnoid spaces may occur, with potentially devastating consequences.

While no one knows for certain how likely it is that pain in the occipital and suboccipital area emanates from the C2–C3 Z-joint and while various studies show greatly disparate findings, several compelling attempts at determining the incidence (a measure of the risk of developing some new condition within a specified period) or prevalence (the total number of cases in the population, divided by the number of individuals in the population) need to be reviewed.

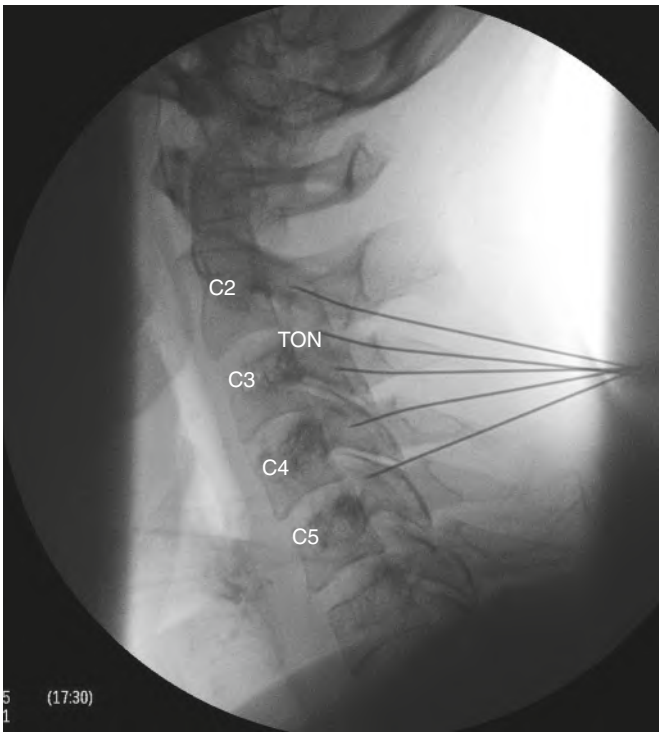
One such study on the role of the cervical zygapophyseal joint in neck pain involved 24 consecutive patients who presented with undiagnosed neck pain and had controlled diagnostic blocks with volume local anesthetic injections.[4] For individuals with occipital or suboccipital headache and neck pain, the lower half of the lateral margin of the C2–C3 Z-joint was selected as the injection site. Complete pain relief was considered to occur if the patients, having received the bupivacaine blocks and then going home to perform their activities of daily living, noted at least 2 h of total analgesia. Failure to derive pain relief resulted in patients undergoing additional cervical medial branch blocks at contiguous levels. Nineteen out of 24 patients had positive results, with nine



• **Figure 64.9** Three needles in place, lateral fluoroscopic view, for C2, C3, and third occipital nerve *(TON)* block, right side. (Figure courtesy of Kenneth D. Candido, M.D.)



• **Figure 64.10** Three needles in place, anterior-posterior fluoroscopic view; right sided C2, C3, and third occipital nerve block (TON). (Photo courtesy of Kenneth D. Candido, M.D.)



• **Figure 64.11** Lateral fluoroscopic image demonstrates placement of 22-gauge, 3.5 inch Whitacre subarachnoid needles at the middle of the waist of the articular pillars for C2, third occipital nerve *(TON)*, C3, C4, and C5 blocks of the medial branches. A single skin wheal has been used for entry of all five needles, minimizing patient discomfort for the performance of the procedure. (Photo courtesy of Kenneth D. Candido, M.D.)

of these ultimately having pain isolated to the C2–C3 level. This would mean that in 47% of patients who had diagnostic block-proven cervical Z-joint pain, the TON was the nerve responsible for mediating the pain. Although this study has not been replicated, it is tempting to use this information as a general rule of thumb when approaching individuals with neck pain resulting from degenerative disease of the cervical spine and when planning nerve blocks based upon the correlation of symptoms with joint pain maps.[5,6] If it is known that in one-half of cases, the level responsible for a given pain problem is at the C2–C3 joint, then it might save time, expense, and patient discomfort to rapidly move toward ruling in or ruling out that level and the TON at the outset as part of the diagnostic workup. However, as noted below, these figures may be overreaching in terms of the actual prevalence of C2–C3 related pain. While TON block may be performed easily and simply and typically is done with little likelihood of encountering significant complications, side effects do occur commonly. Indeed, any patient presenting for this type of procedure must be duly apprised that successful blockade of the TON (or GON) will likely result in the temporary development of ataxia and some gait unsteadiness. For this reason, bilateral blocks at these levels should likely either be staggered, or else the benefit/risk ratio must be significant enough that performing bilateral blocks is warranted.

The subject of joint pain maps merits special mention, as noted above (Fig. 64.5, previously Fig. 52.5). Multiple attempts have been made to delineate the specific cutaneous area of sensation, and hence pain, invested by each respective facet joint and medial branch.[5-9] In the report by Fukui et al.[8] the site of Z-joint intraarticular injection and electrical stimulation (selected cases) was chosen based upon any focal paraspinal tenderness. They observed that with injections performed at C2–C3 (n = 14), symptoms were referable to the upper posterior cervical region (64%), the occipital region (50%), and/or the upper posterolateral cervical region (50%).[8] Windsor et al.[9] electrically stimulated the cervical medial branches, including the TON in nine patients suffering from chronic neck pain. They used the lateral mid-point of the C2–C3 Z-joint to indicate the location of the TON. Relatively reproducible referral patterns were identified for the TON nerve distribution as well as for the other medial branch nerves studied.[9]

However, what is immediately obvious when reviewing these studies is that there is considerable overlap in the areas served by each of the respective segments, much more so than that observed with attempts at mapping spinal nerve dermatome distributions. This produces a diagnostic conundrum, as it is entirely conceivable when approaching cervical spine pain that even perfectly performed techniques, using standardized and accepted anatomical landmarks, may result in failures to derive anti-nociception with the resultant confusion on behalf of the patient and treating physician.

Since both the intervertebral disc and facet joint are fairly equivalently represented as sources of neck pain (approximately 40% each as sources of neck pain, according to two separate studies), a missed diagnosis might lead a pain physician in the wrong direction when seeking to provide pain relief to a given individual.[10,11] Mapping studies may help pinpoint discrete areas of pain referral sources that are then amenable to local anesthetic blockade and/or radiofrequency lesioning techniques. In one such study, joint maps were created by distending the respective joint capsules at segments from C2–C3 to C6–C7. This was done by sequential injections of contrast media, which could be subsequently identified using fluoroscopy. Each joint was noted to produce a characteristic, distinguishable pain pattern from which pain charts could be constructed (Fig. 64.5, previously Fig. 52.5).[6] Although only four total subjects comprised this evaluation, that number is not too disparate from the original small group of subjects selected to develop the original dermatome charts in neurologically impaired individuals, which has persisted, largely unchallenged, for more than six decades.[12] In 10 subjects who received injections based upon maps such as those derived and described above, 90% had complete concordance of the predicted pain level and the positive response to the blocks.[7] The C3–C4, C4–C5, and C5–C6 levels were most commonly affected, with only 10% (1/10) of patients having pain that was documented to result from processes occurring at the C2–C3 (TON) level. Therefore these percentages are less indicative of the possibility of the C2–C3 level being primarily involved in head and neck pain than they are of alternative levels lower in the cervical spine. However, a study by Barnsley and Bogduk from 1993 demonstrated that, following cervical medial branch injections performed in 16 patients suffering from chronic neck pain, 33% (3/9) patients who had complete pain relief were patients for whom the TON was treated.[13] Thus it remains unclear how likely the TON is to be implicated in individuals suffering from chronic head and neck pain. The closest studies performed to identify the prevalence of TON induced headache and neck pain may have been those performed by Lord and Barnsley et al.[14,15] In the first study, 100 consecutive patients underwent double blind, controlled diagnostic blocks of the TON. On two separate occasions, the nerve was blocked using either lidocaine or bupivacaine. The diagnosis of TON nerve involvement was only made if the double diagnostic blocks both relieved the symptoms, with the bupivacaine injection-induced pain relief outlasting that provided by the lidocaine. The prevalence of TON headache in chronic neck pain following whiplash was found to be 27%, while the prevalence of TON headache after whiplash was noted to be 38%.[14]

In the second study, 50 consecutive patients with chronic neck pain and whiplash injury underwent double blind, controlled diagnostic medial branch blocks using 0.5 mL lidocaine (2%) or bupivacaine (0.5%) randomly. In 12/27 patients (44%), the source of symptoms was identified as being isolated primarily to the C2–C3 Z-joint.[15]

These findings corroborate the impression that although there may be substantial overlap in cutaneous innervations of the central and peripheral nervous systems, these joint maps are essential tools to assist one in determining the appropriate approach to a given pain process in any individual. They also demonstrate variability in assessing the relative incidence and relative prevalence of C2–C3 Z-joint pain, depending upon technique of assessment and use of varying provocation maneuvers to assess the joint and the medial branch nerve (TON).

Rationale for Blocking the Third Occipital Nerve

The TON block is useful in both the diagnostic as well as the therapeutic phase of treating cervicogenic headaches. Evidence of efficacy for both local anesthetic blocks as well as for radiofrequency ablation (RFA) of the cervical medial branches has accrued over the past several decades. Nevertheless, it is only relatively recently that the use of medial branch nerve blocking techniques and RFA techniques have received scientific support in the literature. Indeed, two separate attempts at meta-analysis have shown somewhat disparate results. The first such paper, published in 2001, suggested that radiofrequency neurotomy used for treating pain from the cervical Z-joints after flexion-extension injury was only supported by limited scientific data.[16] However, a mere six total studies satisfied the authors' criteria for inclusion; thus it is entirely possible that the data suffer lack of suitable cohort studies to make a true assessment of its validity. The second review performed in 2007 liberalized the inclusion criteria somewhat and found that the support for medial branch cervical block was moderate (Level III), as was the support for cervical medial branch neurotomy.[17] Here, the authors relied upon the Agency for Healthcare Research and Quality criteria, which included some non-randomized trials. They also incorporated studies from the Cochrane Musculoskeletal Review Group, which were randomized trials. One of the important points noted was that the evidence for performing cervical intraarticular facet joint injections was limited both for short-term as well as for long-term analgesia efficacy. This corroborates Dr. Bogduk's earlier assertions that not only are medial branch techniques more likely to target the real source of pain associated with cervical degenerative facet conditions but also that articular procedures have an inherently high failure rate since there is no guarantee that injected local anesthetic will remain in the confines of the joint (see above).

The rationale for blocking the TON is two-fold:

1) To provide a diagnostic evaluation of the C2-C3 facet joint as the source of pain in the occipital and suboccipital areas.
2) To provide an indication as to whether or not neuroablative techniques applied over that nerve might be fruitful in treating pain on a long-term basis.

The present authors suggest performing double diagnostic blocks using 0.5 mL of local anesthetic solutions, typically 0.5% ropivacaine plain, before undertaking neurotomy of the TON. Ropivacaine is used for two major reasons. It has intrinsic vasoconstrictor properties, and therefore no epinephrine is necessary. It also has a cardiovascular safety profile superior to bupivacaine and poses a less theoretical risk for use in outpatient procedures. Unintentional injection into vascular structures, including the vertebral artery, is less likely to result in serious morbidity when ropivacaine is used, in contradistinction to bupivacaine. Ropivacaine also provides a duration of analgesia that exceeds that provided by shorter acting agents such as lidocaine or mepivacaine. Regarding assessing efficacy, it is likely that longer acting amino-amide local

anesthetics may provide greater information than shorter acting drugs since the effect of the shorter acting drugs may be so fleeting as to provide confusing or inexact clinical information. However, whether or not this is true remains the subject of some clinical controversy.

Double diagnostic blocks have been described for assessing the efficacy of cervical medial branch blocks.[18] Barnsley et al. compared single versus double diagnostic blocks in 55 adult patients having neck pain for longer than three months. They randomly used 0.5 mL of either 0.5% bupivacaine or 2% lidocaine. The duration of analgesia was assessed in a double blind fashion. They found that the false positive rate (a test result that is read as positive but actually is negative; a test that shows evidence of a disease when it is not present) of single-blocks was 27% (16/60).[18] They also found that the most common positive levels were at C2–C3 and C5–C6.[18] Lord et al. found that comparative blocks of the medial branches using either lidocaine, bupivacaine, or normal saline in randomized, double blind, placebo-controlled fashion in 50 patients had a specificity (the statistical probability that an individual who does not have the particular disease being tested for will be correctly identified as negative, expressed as the proportion of true negative results to the total of true negative and false positive results) (TN/TN + FP) of 88%, but only marginal sensitivity (the proportion of individuals in a population that will be correctly identified when administered a test designed to detect a particular disease, calculated as the number of true positive results divided by the number of true positive and false negative results) (TP/TP + FN) (54%).[19] Hence some of the 46% of patients who are not placebo responders would incorrectly be labeled as placebo responders if diagnoses were based solely upon comparative blocks.[19]

Slipman et al. retrospectively reviewed 18 patients with chronic persistent daily headaches lasting a mean of 34 months following whiplash injury who underwent intraarticular C2–C3 facet joint injections.[20] They noted that in 61% of cases, headache frequency diminished from daily to less than three headaches/week. Although this work is retrospective, the results nevertheless demonstrated further rationale for targeting the TON in chronic headache conditions refractory to conventional conservative care and management. Furthermore, since the injections were articular and not at the medial branch (TON), the information gleaned from this report may not be useful in determining candidacy for radiofrequency neurotomy.

Technique for Third Occipital Nerve Block

C2–C3 medial branch (TON) procedures are usually performed with the patient in the prone position using continual live fluoroscopic guidance throughout the injection phase (Figs. 64.9–64.11, previously Figs. 52.9–52.11).[21] A bolster is placed beneath the shoulders and chest to elevate the thorax off of the table and to permit gentle head and neck flexion forward. An intravenous cannula is placed, and vital signs are monitored using standard American Society of Anesthesiologists (ASA) basic monitors. After performing a sterile skin preparation, scout films are obtained of the neck, seeking to identify the scalloped margins of the lateral vertebral bodies. Then, skin wheals are raised over the intended target(s) using a hypodermic needle and 1–3 mL of lidocaine. Using short-beveled, 22-gauge, 2.5–3.5 inch needles, the targeted lateral scalloped margins of the vertebral bodies are advanced upon until bony contact is made. At this point, the fluoroscopy unit is rotated laterally to assess the relationship of the advancing needle tip to the TON target in the center of the C2–C3 Z-joint (see above). The needle tip must be recessed posteriorly away from the C2–C3 intervertebral foramen as well as from the known location of the vertebral artery. If no bony contact has been made and 2 cm of the needle has been placed into the skin, then a reassessment of the approach and direction is undertaken while still in the A-P fluoroscopy mode. Once the needle is appropriately seated on the bone at the target (Fig. 64.4, previously Fig. 52.4), the A-P view is once again undertaken to verify that the needle(s) is in the correct position vis-à-vis the lateral vertebral body margin.

Ultrasound guided approaches are rapidly gaining in popularity for all forms of interventional pain procedures, but most clinicians have not yet reached the level of sophistication to supplant fluoroscopy use for this particular procedure. At this point, aspiration tests are performed to verify the absence of blood or cerebrospinal fluid, and the patient is queried to ascertain that no paresthesia has been elicited. If there are none and vital signs remain stable, 0.5 mL of 0.5% ropivacaine is injected. No glucocorticoid is added to the solution, as Manchikanti et al.[22] have demonstrated little if any value of adding steroid to the blocks. While this one study demonstrated no added benefit of corticosteroid use in diagnostic/therapeutic cervical medial branch injection versus not using steroids, many clinicians continue to employ them in daily practice. It can only be stated that this is an area of some controversy, and if the risk-benefit ratio favors using steroids in a given individual suspected of having an inflammatory component to their pain, then there may be little harm in employing them in judicious doses. After completing the injection phase, the needle(s) is cleared and withdrawn, and a sterile dressing is applied over the injection site. The patient should be observed for no less than 30 min as it is quite common that most patients will become ataxic or unsteady of gait following successfully performed procedures. Discharge instructions should be clear and precisely instruct patients to seek emergency medical care if they develop any delayed onset side effects or complications from the procedure, as unlikely as that may be.

Radiofrequency Neurotomy

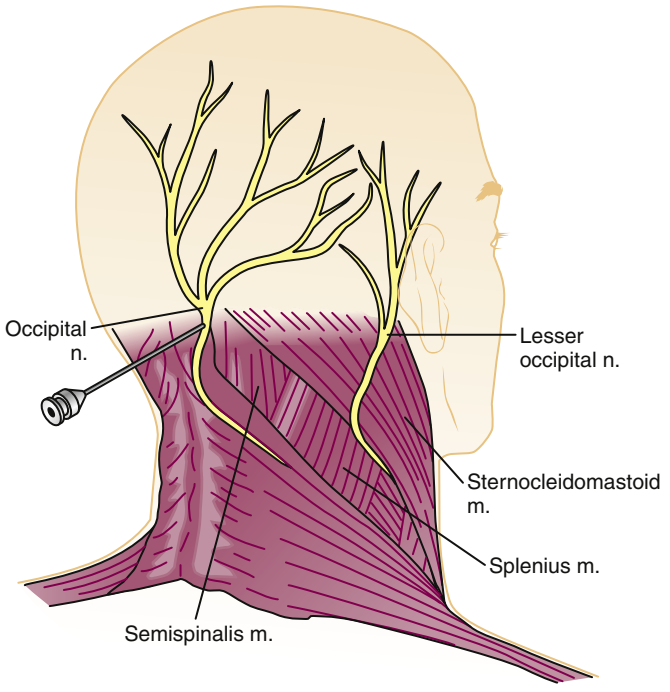
In selected patients, radiofrequency of the TON may be considered for long-term therapeutic benefit. In a study published in 1995, Lord et al. demonstrated the efficacy of performing RFA of the TON in only 40% of patients (4/10), with only three having long-lasting pain relief.[23] They used 10 cm needles with either 4 mm or 6 mm exposed tips. No stimulation test was performed to assure concordance of needle placement with the nerve. Instead, the authors relied solely upon fluoroscopic anatomic cannula placement. The mean duration of the C2–C3 neurotomy procedure was stated to have been 1.5 h.[23] The rather meager success rate was in sharp contrast to the 70% success they noted for lower cervical medial branch procedures. The authors stated that radiofrequency of the cervical medial branches "carries a high rate of technical failure."[23] In 1996 Lord et al.[24] suggested that RFA of the cervical medial branches, performed in 24 patients with a median duration of pain of 34 months following motor vehicle accidents, provided a median duration of analgesia persisting 263 days. This contrasted sharply with the median analgesia of eight days in a control group of patients. However, they excluded individuals with C2–C3 Z-joint pain based upon their rather dismal results from the previous study noted above. In a subsequent study published by the same group of investigators, complete pain relief was found in 71% of 28 patients following

a single RF procedure, persisting a mean duration of 219 days. When failures were excluded from consideration, the mean duration extended out to 422 days (60 weeks).[25] Again, excluded from the study were individuals suffering from TON-mediated C2–C3 pain. Govind et al. in 2003 used three large gauge electrodes to perform RFA procedures of the TON. Following controlled diagnostic blocks, 51 nerves in 40 patients were treated with RFA. Eighty-eight percent (43/49) achieved successful outcomes using this approach, with a median duration of 297 days (42 weeks). Side effects included ataxia, stated to be "slight" numbness, and temporary dysesthesias.[26] Their improved success was attributed to the use of three needles, the use of Ray electrodes instead of SMK electrodes (smaller), and the assurance that each of the three lesions was made at a distance no greater than one electrode width from an adjacent lesion.[26]

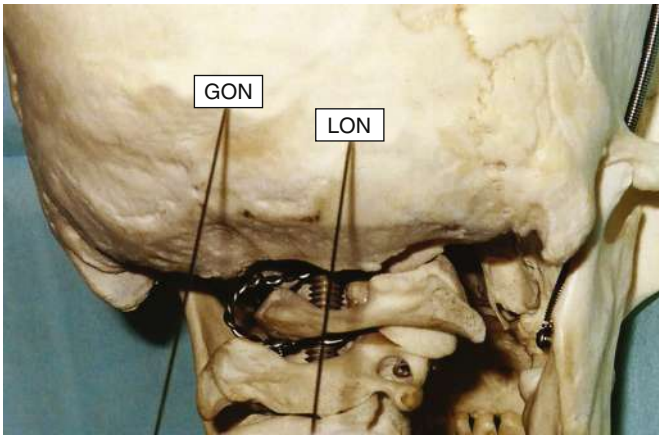
Cohen found that the only factor predicting the success of RFA, defined as at least 50% pain reduction lasting at least six months, was paraspinal tenderness.[27] Although the authors state that C2–C3 pain was included in this analysis, they never indicated how many individuals were treated this way nor what the success rate was for TON RFA.

Greater and LON Blockade (Figs. 64.12 and 64.13, previously Figs. 52.13 and 52.14, and Fig. 64.14).

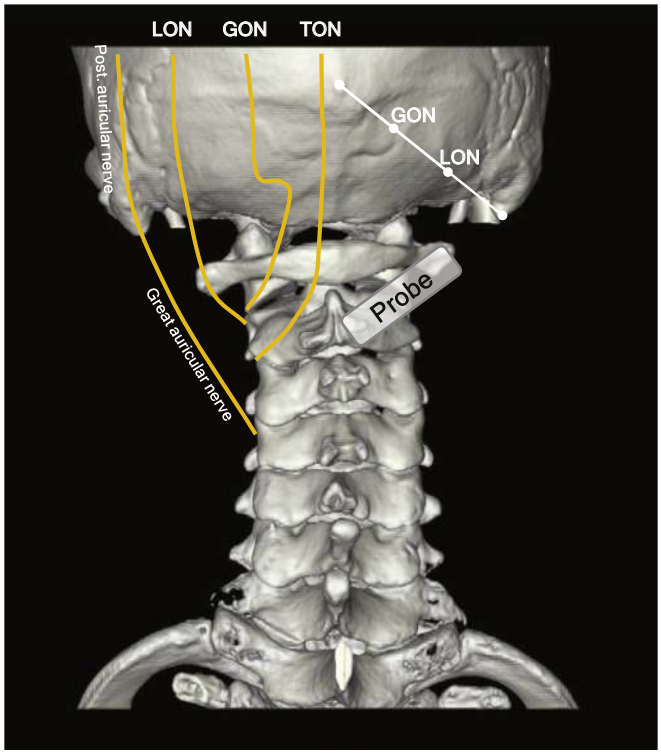
The GON arises from the dorsal primary rami of C2, with occasional contributions from C3. The nerve penetrates the fascia inferior to the superior nuchal crest, where it runs alongside the occipital artery for a variable distance. The sensory area innervated by the nerve includes the medial portion of the posterior scalp, with radiation ventrally up to the vertex. The LON arises from the ventral primary rami of C2 and C3 and passes superiorly and laterally from the occiput to the lateral edge of the sternocleidomastoid muscle. Here the nerve divides into cutaneous branches that innervate the lateral portion of the posterior scalp and the cephalad surface of the ear pinna. Along with the great auricular nerve,



• **Figure 64.12** The anatomy and site of nerve blocking for the greater occipital nerve.



• **Figure 64.13** Needles inserted for right sided greater occipital nerve *(GON)* and lesser occipital nerve *(LON)* blocks. (Photo courtesy of Kenneth D. Candido, M.D.)



• **Figure 64.14** Schematic anatomy of the nerves in the occipital area. *GON,* Greater occipital nerve; *LON*, lesser occipital nerve; *TON,* third occipital nerve.

the GON and LON provide most sensory afferent information for the occipital area and are responsible for transmitting information derived from C2-C3 facet joint derangements to the referral area described.

Occipital nerve blocks have become an increasingly popular method of managing headaches of diverse etiologies, even though the scientific support for doing so is limited. GON blocks have been shown to be ineffective for chronic tension-type headache when prilocaine and dexamethasone were used in a group of 15 patients.[28] They have been used with various degrees of success for postconcussive headaches[29] (80% successful in then patients), atypical orofacial pain,[30] and especially for migraine headaches,

when they are often combined with trigger point injections,[31] or supraorbital nerve blocks,[32] in both cases affording a very high degree of success for ameliorating pain and brush allodynia. A novel use of GON block has been in the successful treatment of patients with abnormal head movements who also suffered from tinnitus and dizziness associated with a previous history of trauma.[33] Further, the injection of botulinum toxin type A (50 units) was suggested to be more effective than the use of bupivacaine in reducing short-term and long-term pain in patients with chronic headache in the occipital area. Although often, the diagnosis of headache because of occipital neuralgia is not too difficult to make,[34] there are cases of refractory headache that require advanced evaluation techniques. Although some suggest performing computed tomography (CT)-guided C2–C3 nerve blocks as a prelude to considering patients who may be candidates for percutaneous rhizotomy,[35] fluoroscopically guided techniques of C2–C3 nerve block have been used and have precluded the requirement to seek more advanced imaging for guidance (Figs. 64.8 and 64.9). Besides, ultrasonography has recently become a more popular image modality for the occipital nerve block at the upper part of the posterior neck, which is named the proximal approach.

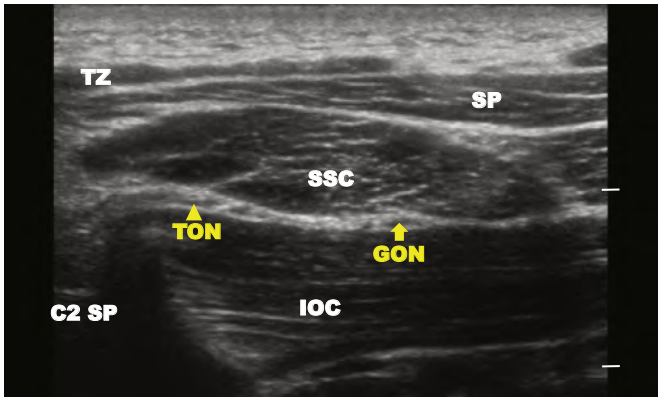
Technique of Blocking the Greater and Lesser Occipital Nerves

Some have erroneously described occipital nerve blocks as merely a field block of local anesthetic and steroid layered somewhere in the posterior part of the occiput, without regard to anatomic landmarks or consequences of errantly placed medications. Indeed, there are cases of sudden unconsciousness reported following LON block, some resulting from occipital artery injection and at least one the result of unintentionally injecting local anesthetic into a previous bone defect from a craniotomy.[36] In addition, it is possible that unconsciousness might occur after the GON block has been made too far inferiorly toward the foramen magnum. Additionally, if practitioners are not careful and discriminating in their choices of frequency of GON block and use judicious doses of agents, including corticosteroids, additional complications like the development of Cushing syndrome may result.[37] Our technique of blockade of the occipital nerves is to perform the procedure with the patient in the sitting position, with the forehead forward, resting on either a Mayo stand, the edge of a padded table, or on a gurney. If possible, the occipital artery is palpated at the superior nuchal ridge. Using ultrasound guidance may help identify the artery, which is often not robust or bounding and, subsequently, not always readily discernible as a distinct structure. As it is virtually impossible to completely disinfect the scalp injection site, we utilize alcohol wipes or a Betadine-soaked pledget to soak the area with a disinfectant prior to inserting the needle, without expectations of complete asepsis. Next, we insert a fine-gauge (25-gauge, 1.5 inch) cutting needle immediately medial to the artery and advance it perpendicular to the skin until the needle tip touches the periosteum (Fig. 64.14). Once the occipital bone has been contacted this way, the needle is retracted about 1 mm and is redirected slightly cephalad. After gently aspirating, 5 mL of local anesthetic (0.5% bupivacaine or ropivacaine) with 4 mg of dexamethasone or 6 mg of betamethasone is injected in a fan-like manner, taking care not to direct the needle too far medially toward the foramen magnum. The LON may be blocked, as can the greater auricular nerve, by removing the needle and placing it into the skin about 3–4 cm lateral to the entry point for GON block, while also directing it inferiorly instead of superiorly as for GON block (Fig. 64.14). After gentle aspiration, 5 mL of the same combination of local anesthetic with or without corticosteroid as noted previously may be injected, again in a fanlike distribution, to block the nerve. After completing GON and LON blocks, it is important to gently massage the tissues of the scalp to assist in the spread of the agents while maintaining pressure over the injection site(s). This will minimize ecchymosis or hematoma formation from this highly vascular area. Often, an ice pack is applied for 20–30 min post-procedure to further minimize swelling and inhibit vascular absorption of the local anesthetic agents, particularly if bilaterally blocks have been performed.

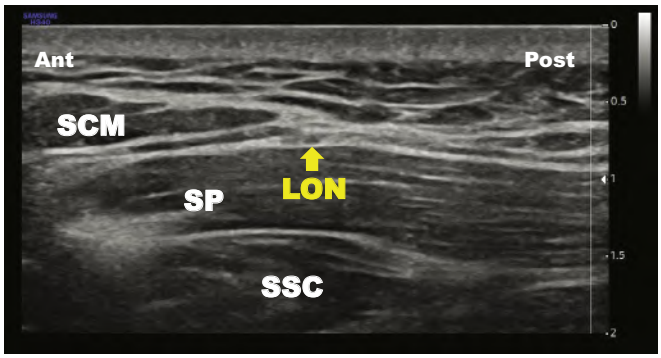
Ultrasound Guided Proximal Approach for the Greater and Lesser Occipital Nerve Block

For ultrasound guided GON block, the patient is asked to be in a prone position with the neck flexed. The first key ultrasonography landmark is the bifid C2 spinous process, where the inferior oblique capitis muscle originates. The linear probe must be located obliquely from the bifid C2 spinous process to the C1 transverse process, where the inferior oblique capitis muscle inserts (Fig. 64.14). The GON is typically identified lying superficial to the inferior oblique capitis muscle and beneath the semispinalis capitis muscle (Fig. 64.15). In this ultrasound image, the third occipital nerve is detected medially to the C2 bifid spinous process. A 22- to 25-gauge, 1.5–3.5 inch needle is introduced from lateral to medial to avoid piercing the tight trapezius fascia via an in-plane approach under real-time ultrasound guidance. While advancing the needle from superficial lateral to deep medial direction, the vertebral artery should not be injured, which is located deeply and medial to the inferior oblique capitis muscle. The needle tip should be visualized in the fascial plane between the inferior capitis and semispinalis capitis muscles. After gentle aspiration, the combination of local anesthetic with or without corticosteroid, as noted previously, may be injected under real-time ultrasound guidance.

For ultrasonography guided LON block, the patient is asked to be in a lateral position. The LON emerges from the superficial branches of the cervical plexus (from ventral rami of C2 and



• **Figure 64.15** Oblique ultrasonography image at the posterior neck for the proximal approach of the GON block. The probe is located between the C2 spinous process and the C1 lateral mass. The greater occipital nerve is detected at the superficial fascial layer of the inferior oblique capitis muscle. *C2 SP*, Spinous process of the C2 spine; *GON*, greater occipital nerve; *IOC*, inferior oblique capitis; *SP*, splenius capitis; *SSC*, semispinaliscapitis; *TON*, third occipital nerve; *TZ*, trapezius.



• **Figure 64.16** Transverse ultrasonography image at the posterior lateral neck. The lesser occipital nerve emerges from the superficial cervical plexus at the upper and posterior margin of the sternocleidomastoideus muscle. *Ant*, Anterior; *LON*, lesser occipital nerve; *Post*, posterior; *SCM*, sternocleidomastoideus; *SP*, splenius capitis; *SSC*, semispinalis capitis.

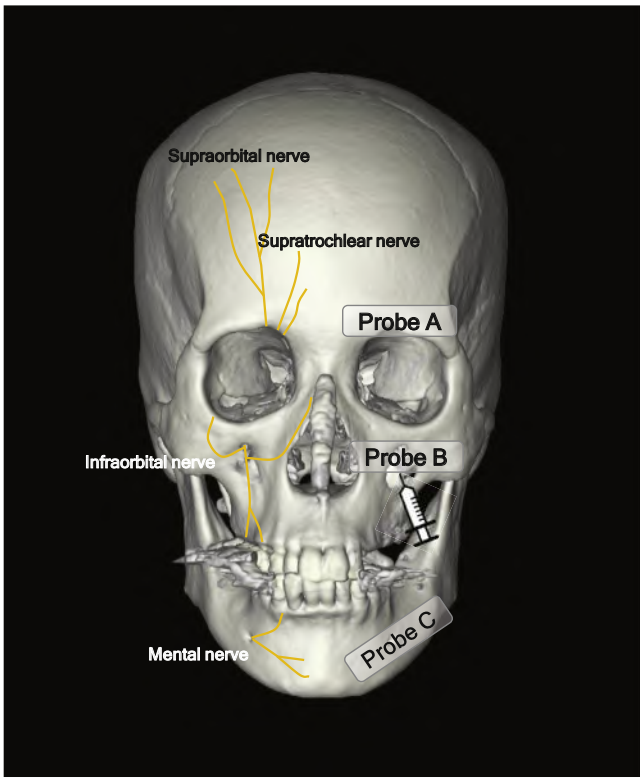
C3). Therefore the first step begins with obtaining the transverse image at the posterior border of the sternocleidomastoid (SCM) muscle, which is seen caudally to the mastoid process. By moving the high-resolution linear probe cranially and caudally along the posterior border of the SCM muscle, the LON is identified as a small hypoechoic oval-shaped structure, which has emerged from the superficial cervical plexus beneath the upper part of the SCM muscle (Fig. 64.16) and runs upward to the lateral occiput. The 25-gauge, 1.5 inch needle is advanced from posterior to anterior (or anterior to posterior) via an in-plane approach. The needle tip should be visualized above the superficial fascial layer of the SCM muscle. After gentle aspiration, the combination of local anesthetic with or without corticosteroid, as noted previously, may be injected under real-time ultrasound guidance.

Facial Pain Nerve Blockades

Supraorbital, Infraorbital, Mental Nerve Blocks (Figs. 64.17 and 64.18)

Peripheral branches of the trigeminal system may be readily accessible through percutaneous needle techniques.

Supraorbital nerve block is useful in the treatment of painful conditions of the frontal nerve, a branch of cranial nerve V1. The nerve leaves the superior orbital fissure to enter the orbit, passing ventrally under the periosteum of the roof of the orbit. The frontal nerve gives off two corollary branches: the supraorbital and the supratrochlear nerves. The supraorbital nerve is larger and more laterally situated than the supratrochlear nerve, and it supplies sensory fibers to the forehead, upper eyelid, and anterior scalp. The nerve is typically blocked by injecting a small volume of dilute local anesthetic, with or without corticosteroid added, into the supraorbital notch (foramen). A 22- to 25-gauge, 1.5 inch needle is typically employed for the block, which is readily accomplished once the notch is palpated and after a sterile skin prep is performed. The goal of needle insertion is to avoid placing the needle tip through the notch, which would assuredly elicit paresthesia of the supraorbital nerve as it pins the nerve against the periosteum. It is more desirable to guide the needle toward the foramen, and, once periosteum is contacted, the needle should be slid slightly medially so that its tip is abutting the rim of the foramen. Following a negative aspiration, 3–4 mL of local anesthetic with 2 mg of dexamethasone

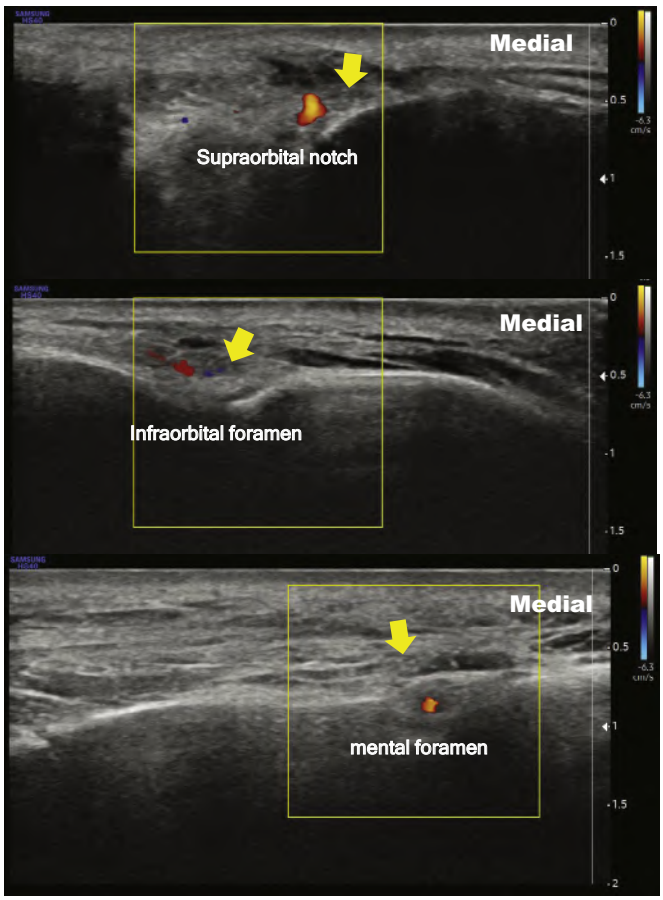


• **Figure 64.17** Schematic anatomy of the nerves on the face and the locations of the transducer (probe) to block each branch.

or 6 mg of betamethasone may be incrementally injected. The needle should be flushed and withdrawn, and a dressing should be applied over the injection site. Supraorbital nerve block has been successfully employed in the treatment of hemicrania continua.[38] Supratrochlear nerve block may be performed at a point slightly medial to the insertion site described earlier for supraorbital nerve block, using the same needle type and volumes and concentrations of local anesthetics and adjuvants. The indications, contraindications, complications, and side effects of this block are virtually identical to those mentioned above.

For the ultrasound guided supraorbital nerve block, the patient is asked to be in a supine position. A target point is usually at 1/3 of the ipsilateral supraorbital margin, where the supraorbital notch could be identified. Using the 6–13 MHz linear transducer, a transverse image is obtained by gently adjusting and tilting the transducer up and down around the eyebrow, whereby the supraorbital notch is revealed on the ultrasound image (Fig. 64.18A). The supraorbital nerve emerges from the superficial notch with the supraorbital artery when the power Doppler mode is used. A short length of needle can be introduced using an out-of-plane or an in-plane approach. After gentle aspiration, the combination of local anesthetic with or without corticosteroid, as noted previously, may be injected under real-time ultrasound guidance.

Infraorbital nerve block is used to block the peripheral contribution of the maxillary nerve, typically affected by conditions of chronic facial pain such as those resulting from complex regional pain syndrome and occasionally herpes zoster. The infraorbital nerve enters the orbit via the infraorbital fissure and passes along the floor of that structure in the infraorbital groove. It exits the skull through the infraorbital foramen, innervating the lower eyelid, lateral nose, and part of the superior lip. A branch of the nerve,



• **Figure 64.18** Transverse ultrasonography images of the trigeminal nerve branches. **Upper** (Probe A)**.** The supraorbital artery *(red)* and nerve *(yellow arrow)* emerge from the supraorbital notch. **Middle** (Probe B)**.** The infraorbital artery *(red)* and nerve *(yellow arrow)* emerge from the infraorbital foramen. **Lower** (Probe C). The mental nerve *(yellow arrow)* emerges from the mental foramen with the inferior alveolar artery *(red)*.

the superior alveolar nerve, innervates the upper incisors, canine, and contiguous soft tissue.

Infraorbital block is performed with the patient in the supine position and the head maintained in a neutral position. The infraorbital foramen is palpated, and a mark is placed over it using a marking pen. A sterile skin prep is performed, after which a fine-gauge (25- or 27-gauge) 1.5-inch needle is advanced into the foramen while maintaining a slight medial direction of the advancing needle tip. This maneuver minimizes the pinning of the infraorbital nerve against bone and potentially traumatizing the nerve. Even taking such precautions, the nerve may be stimulated, resulting in paresthesia to the teeth or lateral naris. After aspirating for the presence of blood, a small volume (3 mL) of local anesthetic, with or without a nonparticulate corticosteroid, is incrementally injected. After clearing the needle, it is withdrawn, and a small bandage is applied over the injection site. The patient should be observed for 20 min and examined for an expanding hematoma of the face, which, if present, is usually readily treated with pressure and occasionally with an ice pack.

For ultrasound guided infraorbital nerve block, a transverse image is obtained to identify the infraorbital nerve exiting from the infraorbital foramen (Fig. 64.18B). The infraorbital nerve emerges from the foramen with the infraorbital artery when the power Doppler mode is used. Because the axis of the infraorbital foramen is oriented caudally and medially, a lateral to medial approach is recommended to reduce the risk of penetration of the foramen. The short length of the needle can be introduced in the lateral to medial direction using the in-plane approach to target the infraorbital nerve. After gentle aspiration, the combination of local anesthetic with or without corticosteroid, as noted previously, may be injected under real-time ultrasound guidance.

Inferior Alveolar (Mental) Nerve Block

The inferior alveolar nerve is a distal branch of the mandibular nerve. The nerve exits the mental foramen at the level of the second molar tooth, having divided into an incisor branch and a mental branch. After exiting the foramen, the nerve sends a ramus superiorly, innervating the lower lip, inferior oral mucosa, and the chin (mental branch). This nerve block has been used in the treatment of mental neuralgia, facial herpes zoster, and cases of trigeminal neuralgia (TGN) of the V3, where the nerve is readily accessible for cryolesioning.[39] There is both an extraoral and an intraoral technique of mental nerve block. The intraoral technique is less painful for patients and provides a similar degree of successful block than the latter agent.[40] When evaluated in 123 patients using a standardized alveolar nerve block method, the block provided analgesia/anesthesia to the first molar (92%), first premolar (55.3%), and canine (38.2%) teeth of the lower jaw.[41] Additionally, levobupivacaine 0.5% with epinephrine 1:200,000 (5 μg/mL) was shown to be equipotent and equally effective to the same concentration and dose of bupivacaine when used for inferior alveolar nerve block. Because of its inherent reduced systemic and cardiac toxicity, levobupivacaine may replace the latter agent for peripheral nerve blocks of the trigeminal system.[42]

Inferior alveolar nerve block is performed with the patient in the supine position and the head maintained in a neutral position. After palpating the mental foramen and performing a sterile skin prep, a small (25- or 27-gauge) 1.5 inch needle is advanced toward the foramen using a slight medial approach, as noted earlier for infraorbital nerve block, to minimize the likelihood of pinning the exiting nerve against periosteum. Using the 6–13 MHz linear transducer, a transverse image shows the mental nerve exiting from the mental foramen with the inferior alveolar artery when the power Doppler mode is used (Fig. 64.18C). Paresthesia may nevertheless be obtained while performing the needle insertion, and patients need to be appraised of this possibility. After a negative aspiration test, 3 mL of local anesthetic with or without a nonparticulate corticosteroid are incrementally injected using a blind technique or under real-time ultrasound guidance. The needle is cleared and withdrawn, and a small bandage is applied over the injection site. The patient should be observed for approximately 20 min to guard against the development of a hematoma, which is typically amenable to compression or the application of an ice pack.

Sphenopalatine Ganglion Blockade

The sphenopalatine ganglion (SPG) is also referred to as the pterygopalatine ganglion, nasal ganglion, or Meckel's ganglion. It represents the largest collection of neurons outside of the brain and inside the calvarium. It has long been targeted for its role in the generation of trigeminal autonomic cephalgia. This broad term includes cluster headaches, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attack with conjunctival injection and tearing (SUNCT). The SPG contains

both sympathetic and parasympathetic pathways, dysfunction of which can cause acute migraine headaches, posttraumatic headaches, and facial neuralgias, including Sluder's, Vail's, and Gardner's syndromes.[43–45] In addition, irritation of the SPG may also result in facial and neck pain because of its connection with the facial nerve, lesser occipital nerve, and cutaneous cervical nerve. The superior cervical ganglion connects to the SPG through the sympathetic trunk, explaining its role in treating head, face, neck, and upper back pain.[46]

The ganglion resides in the pterygopalatine fossa. The fossa is bordered anteriorly by the maxillary sinus, posteriorly by the medial pterygoid plate, medially by the palatine bone, and superiorly by the sphenoid sinus. The pterygomaxillary fissure allows passage of a needle into the fossa, whereas the pterygopalatine foramen is medial to the ganglion and posterior to the middle turbinate. The fossa is approximately 1 cm wide and 2 cm high and resembles a V-shaped vase on a lateral fluoroscopic image. The SPG is covered by a 1–1.5 mm thick layer of connective tissue and mucous membrane and is approximately 5 mm in size and triangular in shape. A large venous plexus overlies the fossa. Foramen rotundum and the pterygoid canal are located on the superolateral and inferomedial aspects of the fossa, respectively. The maxillary artery resides in the fossa. The ganglion is "suspended" from the maxillary nerve by the pterygopalatine nerves and is medial to the maxillary nerve. Posteriorly the ganglion is connected to the vidian nerve, which is formed by the deep petrosal (sympathetic from the upper thoracic spinal cord) and greater petrosal (parasympathetic from the superior salivatory nucleus) nerves. The ganglion has efferent branches and forms the superior posterior lateral nasal and pharyngeal nerves. Caudally, the greater and lesser palatine nerves exit the ganglion. Sensory fibers arise from the maxillary nerve, pass through the SPG, and innervate the upper teeth, nasal membranes, soft palate, and some parts of the pharynx. A small number of motor nerves are believed to travel with the sensory trunks.

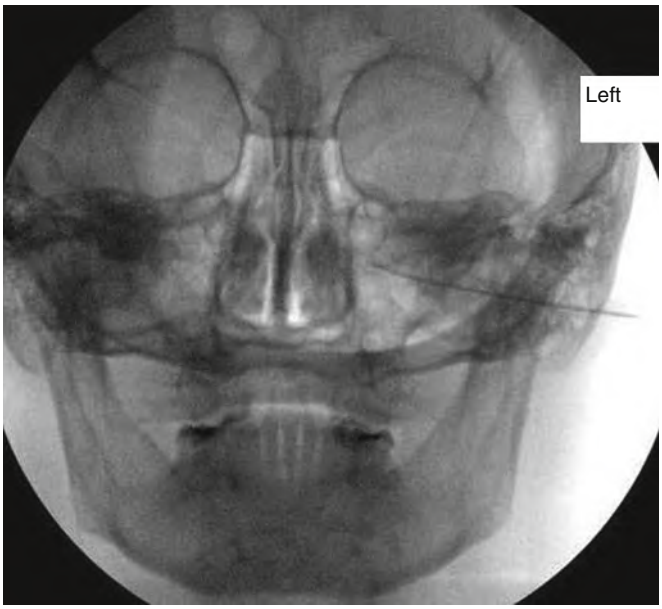
Nerve Block Techniques

There are several techniques to block the SPG, one of which is the topical application approach. With the patient in the supine position and the head maximally extended, as in the sniffing position, the practitioner applies 3 mL of 4% viscous lidocaine, or a long acting local anesthetic, absorbed onto cotton-tipped pledgets. The pledgets are advanced slowly and deliberately to minimize the chance of causing epistaxis in a direction that is directly perpendicular to the floor. The path taken with the pledgets is along the superior border of the middle turbinate of each nostril until the tip contacts the mucosa overlying the SPG. The pledgets are left in place for 30 min while the patient's vital signs are monitored, and then they are removed and discarded. Side effects are typically related to iatrogenic epistaxis, as local anesthetic toxicity is exceedingly rare using this approach.

Another technique is the infrazygomatic approach to SPG blockade, which can be technically challenging. It can be performed without fluoroscopy, but fluoroscopic guidance is highly recommended, as this will anecdotally improve the success of the block and the speed at which it is performed and will decrease potential complications. Noninvasive monitors should be used to record vital signs. Place the patient in the supine position. Sterilely prep and drape the appropriate side of the face. Obtain a lateral fluoroscopic image. Palpate the mandibular notch and anesthetize the skin. If the notch is not palpable, identify the notch on a lateral fluoroscopic view. Identify the pterygopalatine fossa (which appears as a "V") on the lateral image and superimpose the right and left fossae. This is accomplished by manipulating the C arm or the head. The block can be performed with a 3.5 inch, 22-gauge, short-bevel needle with the distal tip bent at a 30-degree angle or with a curved, blunt, 10-cm, 20- or 22-gauge needle. The technique described reflects the use of a blunt needle. Anesthetize the skin and insert a 1.25 inch, 16-gauge angiocatheter through the skin and advance until it is just medial to the ramus of the mandible. This can be checked on an A-P image. Pass the block needle through the angiocatheter and advance it medial, anterior, and slightly cephalad. Obtain a lateral image to check the direction of the needle. Your target is the midportion of the pterygopalatine fossa (Fig. 64.19, previously Fig. 52.20). Get an A-P view and advance the needle toward the middle turbinate, stopping when the tip is adjacent to the palatine bone (Fig. 64.20, previously Fig. 52.21). If resistance is encountered at any point, withdraw and redirect the needle. Given the small size of the fossa, frequent A-P and lateral images may be required to redirect the needle. Once in the fossa, inject 0.5–1 mL of nonionic, water-soluble contrast and observe for intravascular spread or intranasal placement of the needle. Once correct placement has been confirmed, inject 1–2 cc of local anesthetic, with or without steroids.

Two therapeutic choices are available after a successful diagnostic block: conventional radiofrequency lesioning (RFTC) and pulsed radiofrequency (PRF). An insulated radiofrequency needle with a 3–5 mm active tip is placed using the infrazygomatic approach. Once in place, sensory stimulation is performed at 50 Hz up to 1 volt. If the tip of the needle is adjacent to the SPG, the patient should perceive paresthesia at the root of the nose at less than 0.3 volts. If the paresthesia is felt in the hard palate, the needle should be redirected cephalad and medial. Paresthesia in the upper teeth indicates stimulation of the maxillary nerve, and the needle should be more caudal and medial. Motor stimulation is not necessary. After appropriate sensory stimulation, RFTC can be performed at 67°C for 90 s times two cycles. Before lesioning, 2–3 mL of local anesthetic should be injected. To avoid inadvertent

• **Figure 64.19** Lateral fluoroscopic image of a 22-gauge, curved, blunt block needle in the pterygopalatine fossa.



• **Figure 64.20** Posteroanterior fluoroscopic image of a 22-gauge, curved, blunt block needle just lateral to the middle turbinate. Sensory stimulation confirmed that the tip of the needle is on the sphenopalatine ganglion.

lesioning of other nerves around the SPG, a 3 mm active tip is a better choice. For pulsed radiofrequency, the size of the active tip is not important as the electromagnetic field is projected from the tip of the needle and not from the shaft. With pulsed radiofrequency, two to four 120 s cycles are performed at 45 degrees. Local anesthetic is not required for pulsed radiofrequency. The choice of whether to do a conventional or a pulsed radiofrequency lesion after a successful block is up to the discretion of the pain practitioner. Bradycardia ("Konen" reflex) has been noted during both conventional and pulsed radiofrequency lesioning and can be prevented with pretreatment with atropine or glycopyrolate.[47]

Trigeminal Nerve Blockade

Trigeminal nerve blocks encompass a set of procedures with emerging benefits in the treatment of facial pain. Classically considered in cases of refractory TGN, this approach has proven effective in acute and chronic settings. Recent prospective work has suggested that pain relief not only occurs quickly but can last on the order of months.[48] While still emerging, the literature to date indicates that complications are extremely rare. Thus while this block is feasible and effective, it requires appropriate patient selection and a thorough understanding of procedural intricacies.

Trigeminal nerve blocks are generally considered for cases of refractory TGN after unsuccessful medical management or surgical decompression. They may also be indicated for patients with acute herpes zoster outbreaks and subsequent postherpetic neuralgia, in addition to cancer palliation and acute facial pain exacerbations. When facial pain has proven chronic, trigeminal neural blockade is used diagnostically prior to neurolysis.

Contraindications to trigeminal blocks parallel those of peripheral nerves, including infection and malformation (e.g. vascular) at the procedure site. No injection should be performed in those patients who refuse or are not fully consented regarding risks and benefits. The physician should proceed with caution in patients on anticoagulant medications for arrhythmias, DVT, and cardiac stents. Coagulopathies may also be seen in those with liver failure or other hematologic abnormalities. Typically, peripheral blockade is avoided in parturients. However, if performed, decreased doses should be used because of increased susceptibility to local anesthetics.

The trigeminal ganglion (or Gasserian ganglion) is the sensory ganglion of the trigeminal nerve (CN V), which lies in Meckel's cave in the middle cranial fossa and gives rise to three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves.

The ophthalmic nerve (V1), a sensory nerve, divides into three branches (lacrimal, frontal, and nasociliary nerves) before exiting the skull and entering the orbit through the superior orbital fissure. It carries sensory information from the forehead, eyebrows, upper eyelids, and anterior area of the nose.[49] The maxillary nerve (V2), a purely sensory nerve, exits the skull through the foramen rotundum, passes through the pterygopalatine fossa, and reaches the floor of the orbit through the infraorbital foramen to become the infraorbital nerve. It carries sensory information from the lower eyelid, cheek, nose, upper lip, upper teeth and gums, palate, roof of the pharynx, and the maxillary, sphenoid and ethmoid sinuses, and meninges.[50] Of note, its blockade is also achieved by the sphenopalatine block (see the previous section). The mandibular nerve (V3), a mixed sensory and motor (for mastication muscles) nerve, exits the middle cranial fossa through the foramen ovale and descends between the lateral and medial pterygoid muscles, posterior to the lateral pterygoid plate. It delivers sensory branches that supply the anterior part of the ear, the temporal area, the anterior two-thirds of the tongue, teeth, mucosa, and bone of the mandible.[51]

The pterygopalatine fossa (PPF) is a pyramidal-shaped space bounded by the maxillary bone anteriorly, lateral pterygoid plate of the sphenoid bone posteriorly, and the orbital apex superiorly. The PPF contains the maxillary nerve (V2), maxillary artery, and sphenopalatine ganglion and communicates with the infratemporal fossa via the pterygomaxillary fissure. Injection in the pterygopalatine fossa will result in a blockade of the maxillary (V2) branch of the trigeminal nerve and sphenopalation ganglion blockade. Injectate placed in the upper part of the PPF can travel posteromedially through the foramen rotundum to reach the Gasserian ganglion in the middle cranial fossa, resulting in blockade of all three branches of the trigeminal nerve.[52]

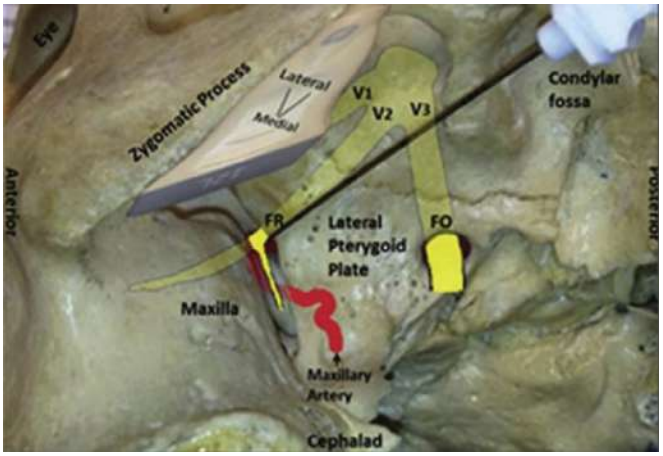
Injection posterior to the lateral pterygoid plate will preferentially block the mandible branch of the trigeminal (V3) nerve

Pterygopalatine Fossa Injection/Maxillary Nerve Block Technique (Fig. 64.21)

Blockade of the maxillary nerve in the PPF can be accomplished with the assistance of both ultrasound and fluoroscopy/CT scan guidance.

Ultrasound Techniques (Fig. 64.22)

Pterygopalatine Fossa injection can be easily performed in a procedure room with the patient in a lateral decubitus position. A 1 mL insulin syringe may be used for subcutaneous topicalization with 0.3–0.4 mL of lidocaine 1%. A 3–5 mL syringe and a 21–22-gauge echogenic needle are commonly used to inject the 5 mL of local anesthetic and steroid mixture. The injectate that may be used includes a mixture of 4 mL bupivacaine and dexamethasone (1 mL). A high-frequency linear array ultrasound is used for



• **Figure 64.21** Skull image illustrating the posterior-to-inferior approach to the ultrasound-guided maxillary nerve block. The ultrasound transducer is placed below the zygomatic bone. The pterygopalatine fossa is anterior to the lateral pterygoid plate. (From Anugerah A, Nguyen K, Nader A. Technical considerations for approaches to the ultrasound-guided maxillary nerve block via the pterygopalatine fossa: a literature review. *Reg Anesth Pain Med.* 2020;45(4):301-305.)

the visualization of superficial structures such as a facial nerve. Other supplies include a sterile probe cover with sterile lubricant. Face-mask and sterile gloves are also recommended.

The patient should be placed in the lateral decubitus position with standard ASA monitoring. After skin preparation, ultrasound is used to identify the lateral pterygoid muscle, the lateral pterygoid plate, and the maxillary bone.

Infrazygomatic Approach

A sterile sheath should cover the transducer probe, which is positioned longitudinally on the side of the face immediately below the zygomatic process, superior to the mandibular notch and anterior to the mandibular condyle.

Posterior to Anterior Approach

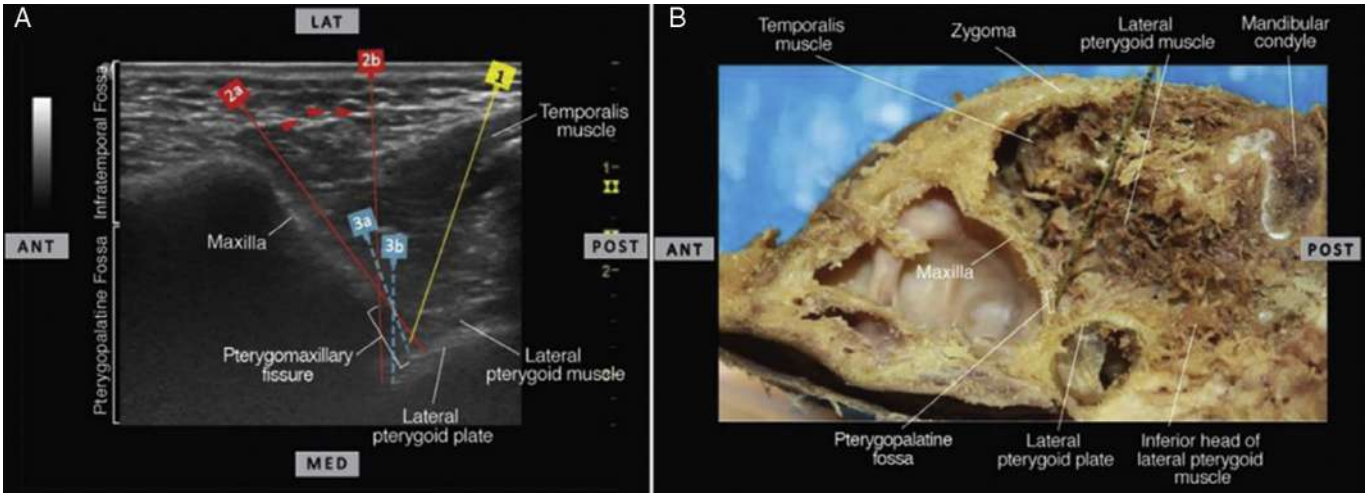
With the infrazygomatic posterior to anterior approach, the needle is inserted in-plane and directed anterior to the coronoid process. The needle is advanced from a posterior to an anterior and a lateral to a medial direction. The tip is placed deep into the lateral pterygoid muscle. The target position is immediately anterior to the lateral pterygoid plate at the pterygomaxillary fissure,[53] and the injectate should be observed passing through the fissure. Caution should be taken to identify the superficial facial nerve and artery and the deep maxillary artery that enters the fossa through the fissure (Fig. 64.23).

Anterior to Posterior Approach

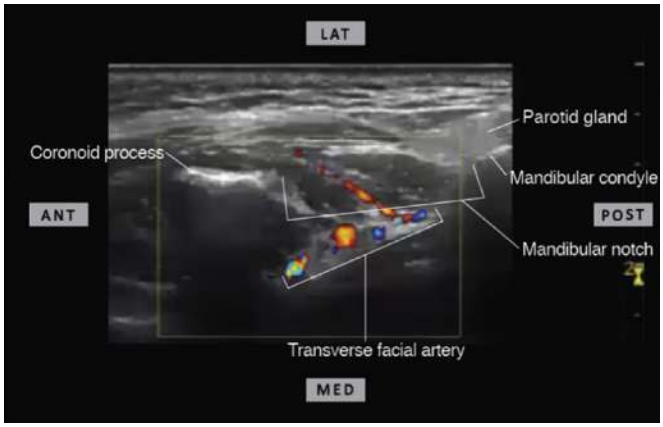
The infrazygomatic anterior to posterior approach is also in-plane. Here, the probe is placed below the zygomatic process, and the needle is inserted toward the area between the uppermost part of the lateral pterygoid plate and the maxillary tuberosity. The provider then advances anterior to posterior and lateral to medial through the lateral pterygoid muscle until contact is made with the lateral pterygoid plate. The needle is carefully withdrawn and directed medially to advance 1–2 mm into the pterygopalatine fossa.[53]

Suprazygomatic Approach (Fig. 64.24)

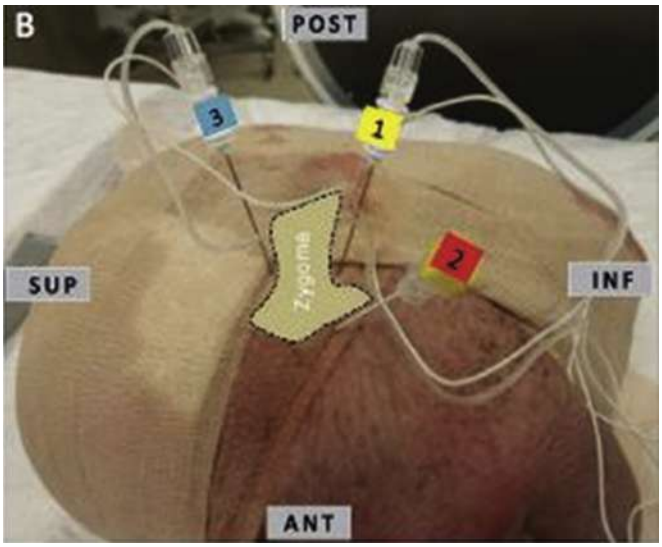
The suprazygomatic approach initially described in the pediatric population[54] utilizes an out-of-plane approach with the ultrasound probe placed below the zygomatic process with an inclination of 45 degrees in the frontal and horizontal planes. The needle is inserted perpendicular to the skin at the area of the frontozygomatic angle above the zygoma. It is advanced to reach the greater wing of the sphenoid at approximately 20 mm depth. The needle is then withdrawn, reoriented, and advanced 35–45 mm deep to the pterygopalatine fossa. Ultrasound guidance in 70% of cases showed LA solution spread into the intermediate (anterior) part and 22% into the deep part of the PPF.



• **Figure 64.22** **A,** Ultrasound image showing the three main approaches and surrounding anatomic landmarks. **B,** Cadaver skull image with needle demonstrating placement through the lateral pterygoid muscle into the pterygopalatine fossa. Yellow needle *(1)* posterior infrazygomatic approach. Red needle *(2)* anterior infrazygomatic approach. *(2a)* shows initial lateral pterygoid plate contact with *(2b)* redirection into the pterygopalatine fossa. Blue needle *(3)* suprazygomatic approach *(3a)* lateral pterygoid plate contact with *(3b)* ion into the pterygopalatine fossa. (From Anugerah A, Nguyen K, Nader A. Technical considerations for approaches to the ultrasound-guided maxillary nerve block via the pterygopalatine fossa: a literature review. *Reg Anesth Pain Med.* 2020;45(4):301-305.)



• **Fig. 64.23** Ultrasound image illustrating the structures surrounding the mandible. (From Anugerah A, Nguyen K, Nader A. Technical considerations for approaches to the ultrasound-guided maxillary nerve block via the pterygopalatine fossa: a literature review. *Reg Anesth Pain Med.* 2020;45(4):301–305.)



• **Figure 64.24** The posterior infrazygomatic in-plane *(1)*, anterior infrazygomatic in-plane *(2)*, and suprazygomatic out-of-plane *(3a)* needle approaches are illustrated. (From Anugerah A, Nguyen K, Nader A. Technical considerations for approaches to the ultrasound-guided maxillary nerve block via the pterygopalatine fossa: a literature review. *Reg Anesth Pain Med.* 2020;45(4):301–305.)

Fluoroscopic Techniques

Maxillary and Mandibular Nerve Blocks

The trigeminal nerve branches may also be blocked using a coronoid approach. The benefit of accessing the V2 and V3 nerves using this approach is the facility in doing so, the ease of reproducibility, and the possibility, albeit not recommended, of doing the procedure absent the requirement for radiologic guidance. The coronoid approach is a useful technique for accessing V2 as it leaves the foramen rotundum. From a technical ease standpoint, coronoid trigeminal block far surpasses the classic technique of Gasserian ganglion block; therefore it is probably our technique of choice in all situations where a V1 block is not essential for diagnosis or management of facial pain.

With the patient in the supine position, the head is turned to the side opposite of the intended block. The coronoid notch is easily identified by asking patients to open and close their mouths and with palpation anterior and inferior to the external auditory meatus. Once the landmarks are identified, the patient is asked to maintain the mouth in a neutral position, while a 22-gauge, 3.5 inch Whitacre or other blunt tipped block needle is advanced perpendicular to the skin of the side of the face, just below the zygomatic arch directly in the center of the coronoid arch. Once the lateral pterygoid plate is contacted (at about 4–5 cm from the skin), the needle is withdrawn about 22 mm. Withdrawing the needle slightly as such improves the likelihood of successfully blocking the mandibular nerve (V3) in addition to V2. A total of 5–10 mL of local anesthetic, with or without corticosteroid, is used for diagnostic/therapeutic block, whereas the same volume of alcohol may be carefully injected using the same approach if neurolysis is desired. The mandibular (V3) branch may be separately blocked here, or it may be blocked in tandem with V2 as described previously. If the nerve is to be blocked, as noted previously for the V2 block, the simplest and likeliest chance for success is via the coronoid approach. If one desires to block the nerve separately, then, once the needle contacts the lateral pterygoid plate, it should be redirected posteriorly and inferiorly until it passes the inferior aspect of the plate. At a point corresponding to approximately 1 cm deeper than the contact point of the lateral pterygoid plate, there will typically be a V3 paresthesia elicited. A usual dose of local anesthetic or neurolytic agent is 3–5 mL using continual, intermittent aspiration tests because of the high degree of vascularity in the area. Because the mandibular nerve (V3) has motor branches, it is not inconceivable that a well-performed local anesthetic or neurolytic procedure might result in paresis or weakness of the muscles of mastication and some facial asymmetry resulting from muscle weakness. This may be more than a nuisance and should be clearly described during the informed consent process with the patient.

Mandibular and maxillary nerve blocks are typically used to ameliorate pain related to TGN, but indications for surgical analgesia include using mandibular block as an adjunct for cervical plexus block for carotid endarterectomy surgery have been described.[55] Although most clinicians continue to use fluoroscopic guidance in most instances of mandibular nerve block, the technique of CT-guided block has been described and may be a suitable alternative if this modality is considered necessary to delineate the relevant anatomy.[56] Continuous catheter techniques of mandibular block have also been described for cancer pain management and analgesia after mandibular fracture repair.[57] Neural complications after mandibular nerve injury are not uncommon and involve the lingual nerve more commonly than the inferior alveolar nerve, often lasting much longer than other common peripheral nerve injuries such as neuropraxia.[58] These injuries may represent neurotoxicity as a central etiology, according to one recent review undertaken in 52 patients who had received these blocks.[59] Otherwise, intravascular injection, hematoma, dizziness, and ataxia occur with some frequency after these procedures and should be discussed with patients during the informed consent process.[60]

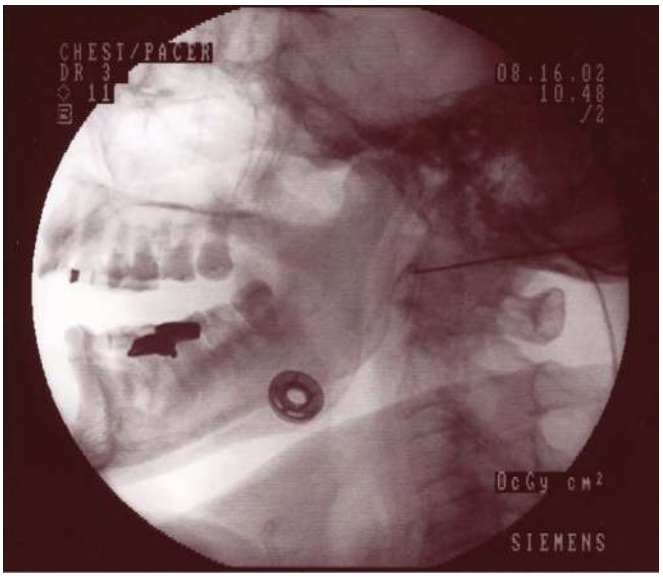
For maxillary nerve block using the coronoid approach, it is important not to advance the block needle more than 0.25 cm once the pterygoid plate has been contacted to minimize the chance of causing neural injury.[61] And as for mandibular nerve block described earlier, a CT-guided technique and a continuous catheter technique of maxillary nerve block have both been described, the former to increase the likelihood of success,[62] and

the latter to extend the duration of analgesia in a group of patients undergoing radical maxillary sinusotomy.[63]

Glossopharyngeal Nerve Block

The glossopharyngeal nerve (GPN) (cranial nerve IX) is infrequently implicated in painful conditions of the face and neck. Nevertheless, because of the lack of familiarity of many pain practitioners with the anatomy and implications of glossopharyngeal nerve dysfunction, it is an important entity to consider in cases of recalcitrant pain, particularly of the tongue, mouth, and pharynx. GPN block may be suitable for conditions such as glossopharyngeal neuralgia and pain from malignancy.[64] The nerve may be affected by tumors of the tongue, hypopharynx, and palatine tonsils. The block is also used during the anatomic evaluation method of differential nerve block. The GPN is a mixed cranial nerve carrying both motor and sensory fibers. The nerve is attached by three or four filaments to the medulla oblongata in a groove between the olive and inferior peduncle. Motor fibers, from cells of the nucleus ambiguus, innervate the stylopharyngeus muscle, while the sensory branches, from cells of the superior and petrous ganglia, innervate the tongue (the posterior third), palatine tonsil, fauces, and mucous membranes of the mouth and pharynx. A branch of the GPN, the carotid sinus nerve, is important in the regulation of blood pressure, pulse, and respiration, as this branch innervates the carotid body and carotid sinus. Sympathetic efferent fibers from the nucleus ambiguus are both preganglionic motor fibers and preganglionic secretory fibers of the sympathetic system. Parasympathetic fibers pass to the otic ganglion, and postganglionic fibers innervate the parotid gland. In conjunction with the vagus and spinal accessory nerves (cranial nerves X and XI), the GPN exits the jugular foramen near the internal jugular vein. All three cranial nerves and the hypoglossal nerve (cranial nerve XII) lie between the internal jugular vein and the internal carotid artery. The styloid process of the temporal bone is a major landmark for successfully blocking the GPN. GPN block is performed with the patient in the supine position, and the head turned slightly opposite to the affected side.

Our practice includes the use of fluoroscopic imaging to help delineate and define the ipsilateral mastoid and the ipsilateral angle of the mandible, as the styloid process is typically found equidistant between those two respective structures. Fluoroscopy also permits real-time imaging of the pattern of injection of contrast media so that in cases where the needle tip has penetrated either the carotid or jugular systems, this activity should be observable and intravascular injection subsequently preventable. Once baseline scout films have been obtained, intravenous access assured, and baseline vital signs documented, the skin overlying the styloid process should be prepped and draped in a sterile fashion. A small skin wheal may be made over the styloid process using a 25-gauge 1.5 inch needle and 1% plain lidocaine, 3–4 mL. Next, a 22-gauge, 1.5–2 inch blunt tipped block needle may be advanced perpendicular to the skin toward the process, aiming for its posterior aspect. The usual depth of contact of the styloid varies from about 1.5–4 cm. Once the needle tip has slipped posteriorly off of the process, 1 mL of iodinated contrast media should be incrementally injected under live continuous fluoroscopy (Fig. 64.25, previously Fig. 52.19). Then, barring any intravascular spread, a short-acting (lidocaine, mepivacaine) and dilute (1% concentration) local anesthetic with epinephrine



• **Figure 64.25** Lateral fluoroscopic image for a glossopharyngeal nerve block. Note that the tip of the needle is at the base of the styloid process.

1:200,000 (5 μg/mL) in a volume of 5–8 mL should be incrementally injected in divided doses. If indicated, a modest dose of nonparticulate corticosteroid (dexamethasone, betamethasone) may be added to the injectate. Patients need to be monitored for a minimum of 30 min following the block to verify that there has been no systemic response to the injected local anesthetic solution. Even taking these precautions and using fluoroscopic guidance does not completely eliminate the possibility of local anesthetic spillover onto the vagus nerve (with resultant ipsilateral vocal cord paralysis, or bradycardia, asystole, reflex tachycardia, and syncope) or the spinal accessory nerve (weakness of the trapezius muscle).

An intraoral approach can also be utilized when there is an anatomic distortion externally by previous surgery or tumor. The patient is placed in a supine position with the mouth wide open, and the tongue is retracted downward and medially using a tongue depressor or a laryngoscope blade. The nerve will be located at the inferior portion of the tonsillar pillar and is accessed via the palatoglossal fold. Once the fold is identified, a topical local anesthetic spray or pledget with 1 mL of saline with epinephrine is applied for hemostasis. A 22- or 25-gauge needle with a slight distal bend (25 degrees) is advanced to a depth no more than 0.5 cm into the mucosa. After negative aspiration, 2–3 mL of local anesthetic (0.2% ropivacaine) with or without steroid is injected. With the intraoral approach, there is a potential for vessel trauma and neurotoxicity, but much less than might occur with the extraoral approach.

Ultrasound-guided Glossopharyngeal Nerve Blockade

For this procedure, the patient should be placed in a lateral position with a thin pillow under the head. The ultrasound probe is used to locate the mastoid and mandibular angle. About 1.5 cm above the posterior edge of the mandibular angle, the probe is used to visualize the styloid process until this image is optimized. Color flow Doppler can be used to identify the internal carotid

artery and vein below or behind the styloid process. Using an in-plane approach, a 22 G 3.5 inch needle is directed for lateral puncture of the mandible. When the tip reaches the styloid process, it is slid back. After negative aspiration, lidocaine 0.5% and methylprednisolone 40 mg are injected with real-time ultrasound guidance.

Summary and Conclusions

With fluoroscopy and especially ultrasound, there has tremendous progress in the performance of these blocks. The safety of these blocks increased as a result. Therefore clinicians should learn and adapt these safer techniques. Additionally, the efficacy of these blocks should be investigated so that their role is firmly established.

Key Points

- Ultrasound-guided greater and lesser occipital nerve blocks are safely and effectively performed for managing some types of head and neck pain.
- Ultrasound-guided supraorbital, infraorbital, and mental nerve blocks should be considered for diagnostic and therapeutic purposes in some types of facial pain.
- Detailed knowledge of the anatomy of the facial structures will improve the success of trigeminal ganglion, sphenopalatine ganglion, and glossopharyngeal nerve blocks.
- There is considerable overlap in the areas served by the upper cervical nerves. It is conceivable that even perfectly performed techniques may result in failures to achieve complete pain relief.
- Expected side effects (e.g. numbness in the distribution of the targeted nerve) versus complications of trigeminal ganglion rhizotomy should be fully explained to and comprehended by the patient before proceeding.
- The use of pulsed radiofrequency for trigeminal-mediated pain syndromes should be considered prior to using thermal radiofrequency after a successful diagnostic block.
- The practitioner should be prepared to treat bradycardia, which is commonly seen with trigeminal and sphenopalatine ganglion procedures.
- Given the complexity of the facial pain syndromes, the sphenopalatine ganglion block should be considered for diagnostic and therapeutic purposes.

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Interlaminar and Transforaminal Therapeutic Epidural Injections

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The International Association for the Study of Pain (IASP) continues to deliberate the classification of chronic pain as a disease symptom or etiology.[1] Semantics aside, pain is undoubtedly a public health crisis as the Institute of Medicine's report estimates that over 100 million American citizens are living with chronic pain.[2] Of this group, chronic low back pain is the most prevalent, and this diagnosis more than doubles a given patient's healthcare expenditures.[3] Besides the higher costs to society, numerous adverse social, emotional, and financial consequences befall the individual patient.[2]

Radiculopathy is a syndrome of neurologic conductive loss (sensory or motor) arising from any compressive force on the nerve root.[4] Radiculopathy is not uniformly associated with radicular pain. Radicular pain, or pain in the distribution of a spinal nerve, is a consequence of inflammation driven by glial production of cytokines and is sometimes termed radiculitis to emphasize the inflammatory component of the disease state.[5,6] Diagnosing radicular insult as the putative source of pain can be challenging, as neither magnetic resonance imaging (MRI) nor physical examination findings correlate precisely with symptom severity or response to treatments.[7–9]

From primary care physicians to spine surgeons, most clinicians concur that conservative non-interventional management is the best initial approach.[10] Because the natural history of radiculopathy secondary to disc herniation is favorable,[11–16] the goal of successful treatment of radicular pain is to reduce pain and restore function while minimizing risk or harm to the patient. Many guidelines exist to guide nonsurgical best practices,[17,18] all of which concur that physical therapy and/or structured exercise programs and oral analgesics should be first line treatments. When these fail, the next step in the management of low back or radicular pain is often epidural steroid injection (ESI).

From 2000 to 2014, the number of injections billed to the United States Medicare system increased to 2.2 million per year. Although total lumbar interlaminar ESI (IL-ESI) and caudal epidural injections decreased by 2% per 100,000 Medicare beneficiaries, this was offset by a 609% increase in lumbar transforaminal ESIs (TFESIs) and 93% increase in cervical epidural steroid injections (CESI) per 100,000 Medicare beneficiaries.[19] Although operative (e.g. spine surgery) management is still far more expensive, two-thirds of non-operative (e.g. ESI) costs can be attributed to spine imaging rather than injection therapy.[20]

Early ESI studies were replete with methodologic deficiencies.[21–23] Many observational studies were encouraging and were only followed by randomized controlled trials (RCTs) that demonstrated no clinical benefit of the evaluated procedure.[24–26] The heterogeneity of studies performed in the lumbar, thoracic, or cervical space further complicates the evaluation of overall epidural efficacy given the anatomic differences between regions of the human spine.

ESIs for treatment of radicular syndromes appear, at the very least, to transiently improve pain.[27] In the short term, ESIs may also have a surgery-sparing effect.[28] As always, patient selection is the most important component of any successful interventional procedure, and providers should carefully assess the patient's history, physical examination findings, and imaging results. This is quite feasible in theory, but the uncertainty surrounding nonsurgical best practices, including concern for serious complications of ESIs,[26,29,30] poses a significant challenge for interventional physicians offering epidural steroid injections to patients.

History

In 1934 Mixter and Barr were the first to suggest that intervertebral disc herniation might be responsible for radicular pain via mechanical compression on the exiting spinal nerve root.[31] Four years before this hypothesis germinated, Evans proposed treating sciatica with injections of 120 mL of 2% procaine via the transsacral canal.[32] Decades later, in 1951, Lindahl and Rexed examined resected dorsal nerve roots from patients with radicular pain and found lymphocytic infiltration and edema, suggesting that inflammation is responsible for radicular symptoms.[33]

Early work in the post-WWII era on injectable corticosteroids (CSs) was a Nobel Prize-winning effort that culminated in the synthesis of the drug hydrocortisone.[34] Soon after, CSs were used in joint injections,[35] and in 1952 Robecchi and Capra reported the first ESI.[36] In the subsequent year, Li'evre et al. described a case series of 20 patients with positive results from epidurally administered hydrocortisone.[37]

Between 1960 and the late 1980s, interlaminar and caudal approaches to the epidural space predominated, largely via non-image guided techniques using surface landmarks and "loss-of-resistance" techniques.[38] In 1988 a study found that a large

percentage of these "blind" epidural injections were either not in the epidural space or were not communicating with the target area of nerve inflammation.[39] In a subsequent review, Johnson and colleagues described 5,489 consecutive image guided injections that resulted in only four complications and only ten patients requiring sedation, thus reassuring providers that ESI procedures could be performed on an outpatient basis. They proposed the use of an epidurogram of contrast dye that allowed more accurate localization within the epidural space while also demonstrating that the injectate reached the target area.[40] In 1986 Benzon discussed the efficacy of ESIs for low back pain and nerve root irritation. He noted that patients with acute radicular pain have better results than those with chronic pain.[41] Although ESIs are most widely performed for radicular pain, they may also be used to treat spinal cysts, spinal fractures, and postherpetic neuralgia[42] and are among the most common procedures performed in pain clinics.[43]

Pathophysiology

Key factors in the provocation of radicular symptoms include mechanical compression of the spinal nerve root or inflammation due to proinflammatory mediators such as prostaglandins and cytokines.[44] CSs, through their anti-inflammatory effects, reduce these inflammatory changes in or around the nerve,[45] thereby decreasing pain and improving function.[12,46]

The nociceptive neural fibers in the outer third of the annulus fibrosus are small unmyelinated C-fibers activated by peptidergic neurotransmitters such as calcitonin gene-related peptide and substance P. In discography-proven pain-generating discs, these nerve fibers sprout farther into the disc, usually accompanied by neovascularization and further degradation of the disc matrix.[47] This *de novo* innervation appears to originate from the vertebral end-plate region, which may be the progenitor of the pathologic pain attributed to the disc itself.[48,49] Modic changes at the end-plate correlate with radiologic spine degeneration but may not have an association with axial or extremity pain.[50] The disc is relatively avascular, and therefore cellular fuel enters and waste exits via passive diffusion. Homeostatic attempts by the body to improve disc nutrition may explain why new blood vessels (and associated nerve fibers) invade the injured disc from the vertebral end-plate region.

The processes that lead to disc degeneration may ultimately lead to disc herniation. Herniated nucleus pulposus results in the local release of cytokines and other inflammatory mediators that cause chemical radiculitis.[51] Burke and associates[52] found increased levels of the inflammatory cytokines interleukin (IL)-6 and IL-8 in disc material taken from patients with known disc disease. Cytokines tumor necrosis factor-α (TNF-α), IL-1α, IL-1β, IL-6, and IL-17 are also thought to promote extracellular matrix degradation, chemokine production, and changes in the intervertebral disc (IVD) cell phenotype, all of which can lead to degeneration of IVD tissues.[51] Olmarker et al.[53] found that the application of disc material onto spinal nerve roots induced functional and morphologic changes in these nerves. In addition, disc cells express TNF-α, which, when applied to spinal nerve roots, causes similar changes to those observed after the application of disc material.[51,54] Selective inhibition of TNF-α reduces the intraneural edema seen in this context,[55] lending further credence to the theory that exposure of the nerve root to disc material can be responsible for radicular pain irrespective of anatomic perturbation.

Epidural Injection Techniques

The approaches used to access the epidural space include interlaminar, caudal, and transforaminal. Published studies and guidelines generally agree that all three approaches afford similar clinical benefits but differ markedly in complication rates.[56–59] For all injections, the patient was placed in the supine position, the skin was cleansed with a chlorhexidine-based solution unless contraindicated, draped in a sterile fashion, and the skin and subcutaneous tissues along the proposed needle trajectory were anesthetized with 0.5%–2% lidocaine. Non-particulate steroids are increasingly used for transforaminal injections due to the risk of arterial thrombosis from particulate steroid introduction.[60] The procedure should be aborted if paresthesia or cerebrospinal fluid aspirate occurs, and these risks will be discussed in greater detail later in the chapter.

Cervical Transforaminal Epidural

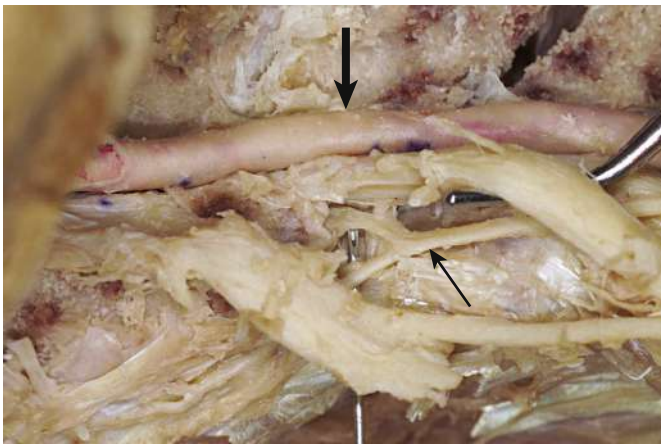
An oblique lateral radiograph is adjusted to maximize the breadth of the intervertebral foramen with the superior articular process (SAP) visualized as a straight line at the posterior aspect of the foramen. A spinal needle was advanced to contact the SAP in the posterior foramen. From the SAP, the needle is "walked off" into the posterior aspect of the foramen, superior to the midpoint. The proceduralist ensures that the needle tip remains superior to the midpoint of the posterior foramina, that is, above the midsagittal plane of the cervical articular pillar in anteroposterior (AP) view, to protect against vascular injury of critical arteries located in the inferior half of the posterior aspect of the intervertebral foramen (Fig. 65.1).[61,62] Local anesthetic (LA) test dosing may be used to rule out arterial location of the needle tip, and digital subtraction imaging should be used to substantiate the absence of vascular uptake prior to CS administration. Although we discuss this technique in this chapter, extreme caution must be applied, and rigorous patient selection and consent are required as the risk of vascular penetration at the cervical level is associated with high morbidity and even mortality.

Lumbar Transforaminal Epidural

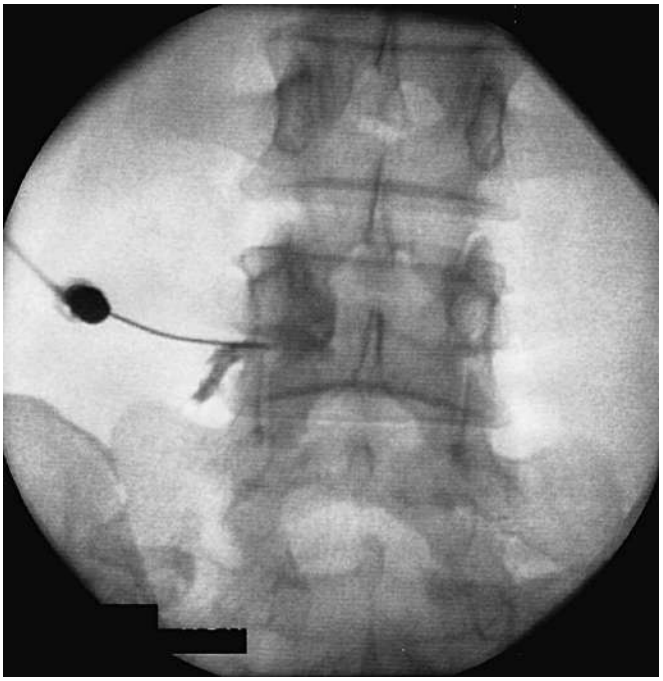
An oblique view is obtained from the lateral surface of the SAP and marked at the six o'clock position along a line that bisects the sagittal plane of the pedicle (Fig. 65.2).[25] Either a cutting-type needle or a blunt needle with a side port opening may be used; some authors contend that a blunt needle may be less apt to enter blood vessels.[63] The needle is advanced incrementally in one of three approaches: the sub-pedicular, the "safe triangle" as proposed by Bogduk and Cherry,[64] or the Kambin triangle (Fig. 65.3).[65] There was no difference in the amount of contrast dye required to visualize epidural spread based on the approach.[66] Injection of contrast medium should demonstrate a neurogram and medial spread into the epidural space (Fig. 65.4). Digital subtraction imaging is useful to substantiate the absence of vascular uptake (Fig. 65.5) as a LA test dosing to detect arterial administration of CSs.

Cervical Interlaminar Epidural

This is most safely performed at the C7-T1 or T1-T2 levels, as the posterior epidural space is 1.5–2 mm greater at these levels than at more superior cervical levels.[67] It is also prudent to review



• **Figure 65.1** Anatomic cadaver dissection demonstrating the vertebral artery (*pink, large arrow*) and the exiting left C5 spinal nerve lifted by the probe. The needle tip is pushing on a spinal branch of the ascending cervical artery (*small arrow*) at the outer aspect of the C4-5 intervertebral foramen.



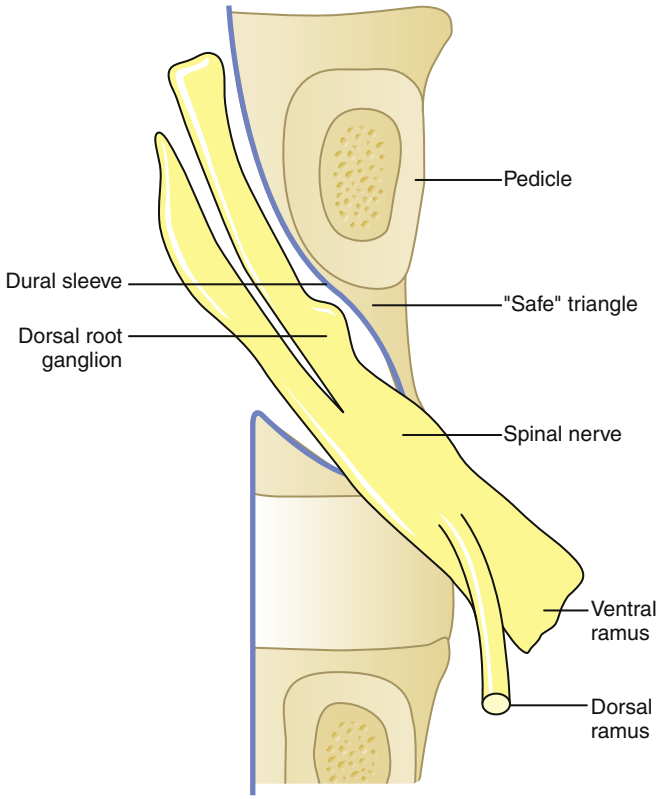
• **Figure 65.2** Needle placement for a left l4 transforaminal epidural block. The needle has been "walked off" the lateral edge of the superior articular process and is at approximately the midsagittal plane relative to the pedicle above.

a patient's MRI prior to the procedure to ensure that the epidural absolute distance is greater than 10 mm at the proposed injection site.[68,69] Caudocephalad angulation of the fluoroscope is used to visualize the interlaminar opening in maximal diameter, and an epidural needle is advanced toward the inferior laminar bone at the target level. After contact with the inferior lamina, the needle is walked superiorly until the needle is superior to the lamina. At this point, a loss-of-resistance (LOR) syringe is attached, and the needle is advanced with the operator correlating the tactile LOR technique with a fluoroscopic view of the lateral or the increasingly popular contralateral oblique orientation (Fig. 65.6).[70]

Resistance to pressure increases as the needle moves toward the anterior extent of the spinous processes, and a subtle LOR will be detected as the tip enters the epidural space, after which contrast dye and CS may be injected. Occasionally, there are discontinuous areas of the ligamentum flavum in the cervical epidural levels,[67] causing the LOR to be more subtle than in the inferior vertebral levels. An alternative technique uses a needle advanced at a 45-degree angle until the epidural space is accessed, after which a catheter can be threaded cephalad through the needle to the target level.[71]

Lumbar Interlaminar Epidural

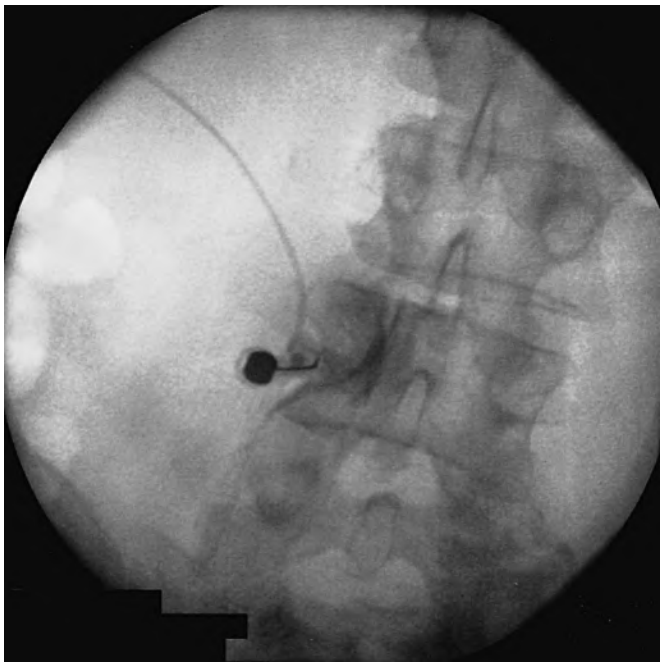
An epidural needle is advanced toward the interlaminar vertebral target, and the epidural space is identified using the LOR technique. The interventional physician may choose to traverse the ligamentum flavum and enter the epidural space in the lateral fluoroscopic view to ensure appropriate placement. Contrast dye demonstrating an epidurogram in both AP (Fig. 65.7) and lateral fluoroscopic views provide support for correct needle placement, after which CS may be administered.



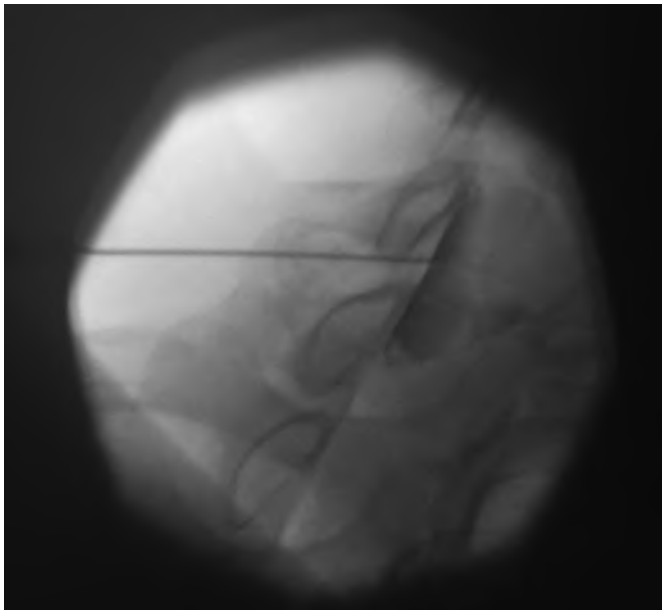
• **Figure 65.3** The "safe" triangle depicts the confines of the classic transforaminal epidural technique. The needle is safely placed inferior to the pedicle's inferior border, superior to the tangentially exiting spinal nerve, and lateral to the dural sleeve.

Caudal Epidural

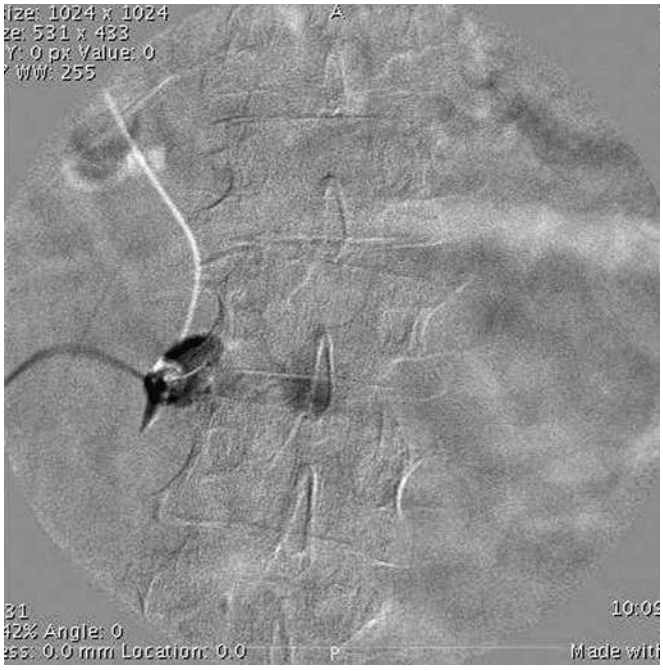
Many techniques have been described for accessing the epidural space via the sacral hiatus. Both cutting and blunt-tipped needles can be used for access, and the procedure can be performed blindly or with fluoroscopic or ultrasonographic guidance. The



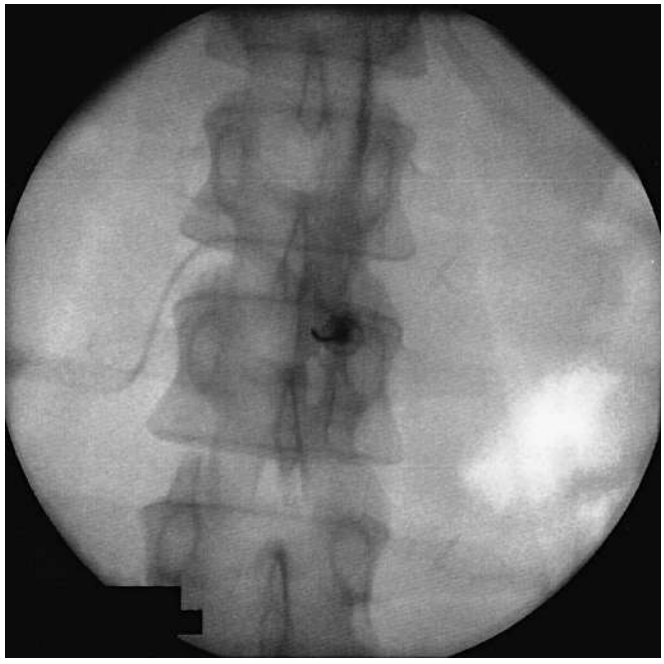
• **Figure 65.4** Spread of contrast dye is seen along the medial border of the pedicle and outlining the exiting spinal nerve.



• **Figure 65.6** An interlaminar cervical epidural procedure demonstrates a characteristic filling pattern along the pedicular column in contralateral oblique fluoroscopic visualization.



• **Figure 65.5** Digital subtraction sequence of a left L2 transforaminal epidural injection. The contrast dye outlines the exiting spinal nerve and displays no vascular uptake despite the high likelihood of proximity to the great segmental medullary artery of Adamkiewicz (see Figure 60.9).



• **Figure 65.7** An interlaminar epidural procedure demonstrates one-sided spread at the same level and cephalad to the injection.

caudal ESI may be performed in patients even after posterior spine instrumentation and is therefore often used for post-surgical patients that will not have a reliable LOR with an interlaminar approach but also have stenosed foramina that cannot safely accommodate a TFESI.

Pharmacology

Corticosteroids (CSs) are key mediators in the maintenance of normal physiology and in the complex adaptive mechanisms that protect an organism amid internal or external stressors.[72] CSs maintain the function and integrity of many physiologic and bio-

chemical processes, including regulation of protein, carbohydrate, and lipid metabolism.[73,74] Naturally occurring CSs are classified into three functional groups: glucocorticoids, mineralocorticoids, and adrenal androgens.[75] Glucocorticoids (GCs) act primarily to enhance the production of high-energy fuel and glucose and to reduce other metabolic activity.[73,76] Synthetic injectable GCs have been used to relieve vertebrogenic, arthritic, and radiculopathic pain.[46]

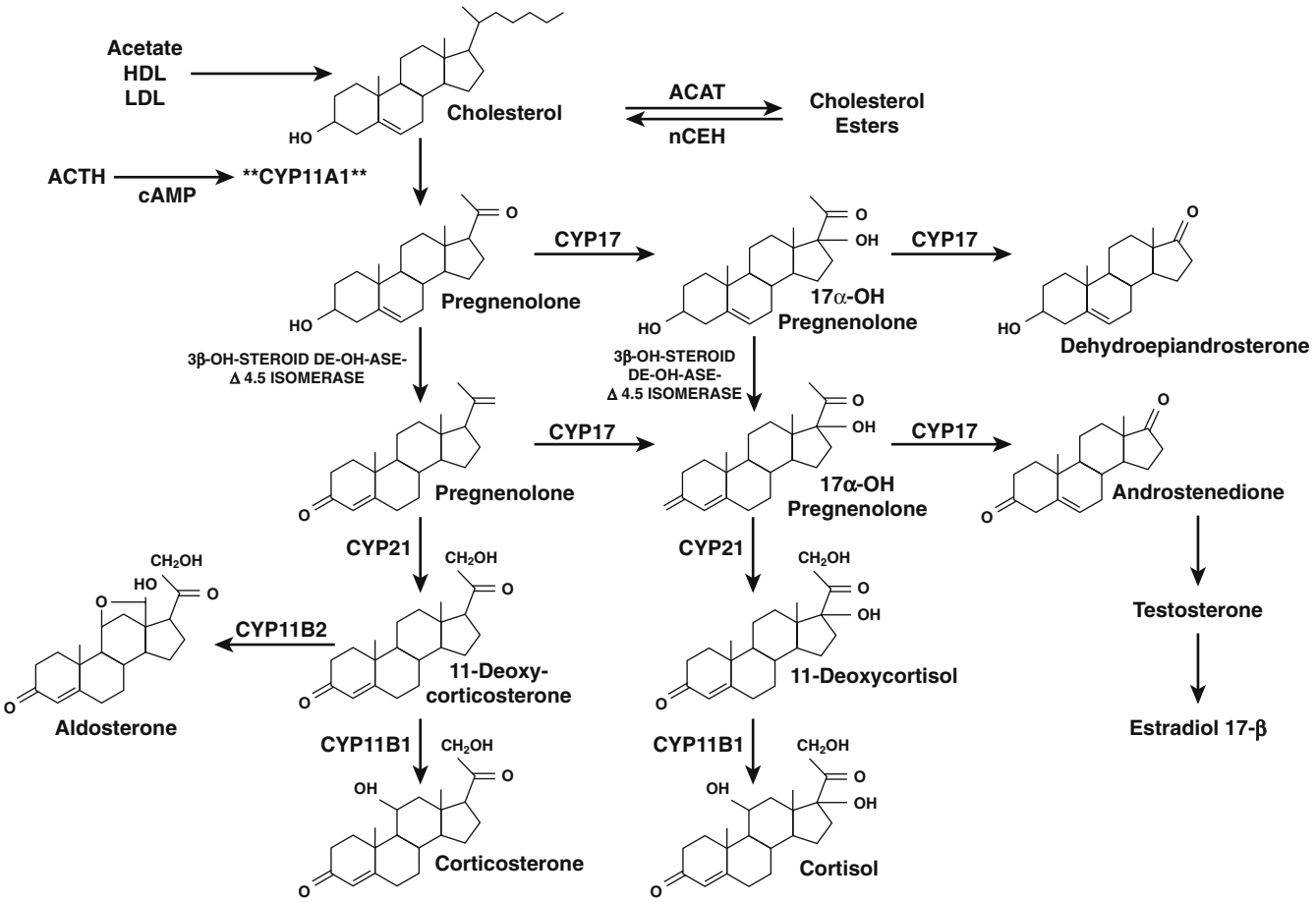
GCs stimulate hepatic gluconeogenesis, increase hepatic glycogen content, and inhibit insulin-mediated peripheral blood glucose uptake. They modulate protein metabolism by decreasing peripheral protein synthesis and stimulating protein catabolism while stimulating protein and enzyme synthesis in the liver.[73] GCs regulate lipid metabolism largely by potentiating catecholamine-enhanced activation of cellular lipase, resulting in lipolysis.[74] Hemodynamically, GCs modulate α-adrenergic receptor synthesis and cell density,[77] prevent α-adrenergic receptor desensitization and uncoupling,[78] and inhibit nitric oxide synthase.[79] Through these mechanisms, GCs maintain vascular responsiveness to circulating vasoconstrictors and, in high doses, may restore circulatory function in shock (hemorrhage, endotoxin, anaphylaxis, trauma). Similarly, in acute inflammation, they maintain adequate microcirculation by reducing capillary endothelial permeability and preventing edema formation.

All CSs are produced in the cortex of the adrenal gland, which comprises three distinct zones.[75,80] GCs are produced primarily by the middle zone, the zona fasciculata, an area occupying over 70% of the cortex, and in smaller amounts by the inner zone, zona reticularis. Cortisol is the primary glucocorticoid and accounts for approximately 80% of GC production. Circulating plasma lipoproteins provide the most cholesterol for steroid synthesis. Cholesterol uptake is upregulated in response to adrenocorticotropic hormone (ACTH) secreted by the pituitary gland. The first and rate limiting step in steroid biosynthesis is the conversion of cholesterol to pregnenolone (Fig. 65.8).[80] Cortisol secretion is controlled by the hypothalamic-pituitary-adrenal (HPA) axis and depends on three factors:

1. Negative feedback by serum cortisol levels. Cortisol exerts a negative feedback inhibition on corticotropin-releasing hormone (CRH) secretion by binding to specific steroid receptors in the central nervous system (CNS).[81] It also inhibits both ACTH secretion and pro-opiomelanocortin (POMC) gene transcription.
2. Circadian pattern. It is estimated that human cortisol production is approximately 5–10 mg/m^2 per day.[82,83] This amount is equivalent to 20–30 mg/day of hydrocortisone or 5–7 mg/day of oral prednisone.[82] Peak levels of ACTH and cortisol secretion occur between 4 a.m. and 8 a.m., with the lowest levels of secretion occurring between 8 p.m. and 12 a.m.[75]
3. The CNS controls secretion. During non-stress periods, cortisol production is influenced by CNS activation, CRH, and ACTH release, which vary based on baroreceptors, chemoreceptors, nociceptors, and emotional afferent signals. Baroreceptor and chemoreceptor afferent inputs to the medulla are transmitted via the pons to the hypothalamus. Nociceptive afferent signals activate the medulla and thalamus, which, along with emotional triggers, directly activate the hypothalamus via the paleocortex limbic system. The activated hypothalamic paraventricular nucleus then stimulates the synthesis of CRH, which is secreted into the hypophyseal portal system to the anterior pituitary, causing ACTH release.[81] Cortisol can increase 5- to 10-fold during stress, to a maximal level of approximately 100 mg/m^2 per day.[75,84]

Cortisol circulates in the blood in three forms: the physiologically active free cortisol (5%), cortisol bound to CS binding globulin (CBG) (90%), and the remaining 5% as cortisol bound to albumin or cortisol metabolites.[73] CBG, also known as transcortin, has a high affinity for cortisol but is present in small amounts, while albumin binds cortisol with less affinity but is abundant. Total cortisol blood levels, including the unbound percentage, increase during stress.[81] CBG levels increase in high-estrogen states, during pregnancy, and during the administration of contraceptives.[73] Most synthetic GCs have less affinity for CBG (approximately 70% binding), leaving more free cortisol. As a physiologically active form, this explains their propensity to produce cushingoid symptoms even at low doses. Cortisol is metabolized in the liver, with subsequent renal excretion of metabolites. Stress due to physical (trauma, surgery, exercise), psychological (anxiety, depression), or physiologic (hypoglycemia, infection) origin increases cortisol levels within minutes. Similarly, pain, fever, and hypovolemia cause a sustained increase in ACTH and cortisol secretion.[84] An increase in ACTH and cortisol levels in response to surgery persists for 24–48 h and is associated with the extensiveness of the procedure. Adult adrenal glands produce approximately 50 mg of cortisol/24 h during minor surgeries and 75–150 mg/24 h during major surgeries.[85] The mechanism of the HPA axis, when stimulated to produce cortisol, is the body's response to elevated levels of circulating cytokines, appearing within minutes of trauma/surgery. CSs improve survival in stress by reducing the duration of shock, decreasing the severity of inflammation, improving vessel contractility and hemodynamics, and preventing inflammatory cell recruitment, proliferation, and release of pro-inflammatory mediators.[86]

CSs are predominantly used in interventional pain management because of their anti-inflammatory effects and temporary relief of pain symptoms. Mechanisms include effects on cytokines, inflammatory mediators, inflammatory cells, nitric oxide synthase, and adhesion molecules. Cytokines are important mediators of inflammation, and the pattern of their expression largely determines the magnitude and persistence of the inflammatory response.[87] Steroids have potent inhibitory effects on cytokine transcription and synthesis, especially those relevant to chronic inflammation (IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, and granulocyte-macrophage colony-stimulating factor).[88,89] They also inhibit the synthesis of the IL-2 receptor and oppose the induction of IL-2 and T-lymphocyte activation and proliferation. The primary anti-inflammatory effect of steroids appears to be the suppression of transcription of genes involved in inflammation such as collagenase, elastase, plasminogen activator, cyclooxygenase (COX)-2, prostaglandin E_2 (PGE_2), phospholipase A_2, and most chemokines.[90,91] In addition, GCs interfere with macrophage activity by impairing phagocytosis, intracellular digestion of antigens, and release of IL-1 and TNF-α.[73] By inhibiting chemokine expression, GCs prevent the activation and recruitment of inflammatory cells, including eosinophils, basophils, and lymphocytes.[90] By increasing lipocortin (annexin) 1, a phospholipase A_2 inhibitor, GCs decrease the production of inflammatory mediators such as leukotrienes, prostaglandins, and platelet-activating factor and upregulate transcription of anti-inflammatory genes.[89,91–93] In addition, GCs cause an expansion in the number of circulating neutrophils secondary to decreased adherence to vascular endothelium,



• **Figure 65.8** Steroidogenesis in the adrenal cortex. Conversion of the cholesterol to pregnenolone is the rate limiting step in the synthesis of glucocorticoids. *ACAT*, Acyl coenzyme A cholesterol acyl transferase; *ACTH*, adrenocorticotropic hormone; *CYP11A1*, 20α, 22R-hydroxylase cholesterol side chain cleavage; *CYP11B1*, 11-β hydroxylase and 19-hydroxylase activity; *CYP11B2*, aldosterone synthase; *CYP17*, 17-α hydroxylast and 17-20 lyase activities; *CYP21*, 21-hydroxylase; *HDL*, high-density lipoproteins; *LDL*, low-density lipoproteins; *nCEH*, neutral cholesterol ester hydrolase. (Reproduced and modified from Rosol TJ, Yarrington JT, Latendresse J, et al. Adrenal gland structure, function, and mechanisms of toxicity. *Toxicol Pathol*. 2001;29(1):41–48.)

termed demargination, and stimulation of bone marrow production.[94] GCs inhibit the production of T lymphocytes by down-regulating T-cell growth factors IL-1β and IL-2, and they inhibit the release of various T-lymphocyte cytokines.[73] GCs suppress ectopic neural discharge in neuromas or severed nerves,[95] and the topical application of methylprednisolone blocks transmission of C-fibers but not the A-β fibers.[96] This suggests a direct neural membrane stabilizing effect. Last, GS receptor sites have been found on 5-hydroxytryptamine (5-GC) and noradrenergic neurons within the dorsal horn substantia gelatinosa. These are known pathways of pain transmission and suggest that CSs may modulate nociceptive transmission via direct action on the spinal cord.

Several synthetic steroid preparations are available and are widely used in interventional pain procedures. They vary in anti-inflammatory potency, mineralocorticoid activity, solubility, and duration of action. Short-acting synthetic steroids, such as hydrocortisone and the inactive cortisone (converted by the liver to the biologically active cortisol), have durations of action of 8–12 h; the intermediate-acting steroids, prednisone, prednisolone, methylprednisolone, and triamcinolone, have durations of action of 24–36 h. The longest acting steroids, dexamethasone and betamethasone, have durations of action longer than 48 h. Although the choice of steroid used by interventional pain physicians is frequently based on anti-inflammatory potency and duration of action, the steroid particulate size and potential for aggregation have become major determinants of CS selection given reported catastrophic neurologic sequelae. Table 65.1 summarizes the properties of commonly used injectable CSs.

Corticosteroid Alternatives

Because CSs have dose limitations and side effects, many researchers are interested in the systemic or epidural delivery of specific anti-inflammatory agents as an alternative therapy. Korhonen and colleagues[97] used intravenous infliximab, a TNF-α inhibitor, to treat patients with disc herniation and radicular pain and found that pain scores were reduced at the one year follow up when compared with controls. Etanercept, another TNF-α inhibitor, has also

TABLE 65.1 Properties of Commonly Used Injectable Corticosteroids[a]

Steroid	Commercial Name	Equivalent Potency (mg)	Relative GC Potency	Solubility	Maximum Particle Size (microns)	Particles >10 microns (%)	Particle Aggregates
Methylprednisolone acetate	Depo-medrol, Solu-medrol	4	5	0.001	>500	45	Extensive
Triamcinolone acetonide	Kenalog	4	5	0.0002	>500	45	Extensive
Betamethasone acetate, Betamethasone sodium phosphate	Celestone soluspan, Betaject	0.75	33	Acetate form-"practically insoluble." Sodium Phosphate form-freely soluble	500	35	Some
Dexamethasone sodium phosphate	Decadron phosphate, Adrenocort, Decaject	0.75	27	Freely soluble	0.5	0	None

[a]Reproduced and adapted from MacMahon PJ, Eustace SJ, Kavanagh EC. Injectable corticosteroids and local anesthetic preparations: a review of radiologists. *Radiology*. 2009;252(3):647-681. Benzon HT, Chew TL, McCarthy RJ, et al. Comparison of the particle sizes of different steroids and the effects of dilution. *Anesthesiology*. 2007;106(2):331-338 and HT Benzon, SN Raja, et al. (eds). *Essentials of Pain Medicine*. 2017.

shown promising efficacy as a systemic treatment for lumbosacral radicular syndromes.[98] Cohen and associates[99] performed a novel RCT evaluating patients with subacute lumbosacral radiculopathy that showed significant patient improvement with epidural etanercept. However, a follow up multicenter RCT showed that epidural etanercept did not improve pain compared to steroids or placebos.[100] A subsequent well-conducted RCT demonstrated that epidural etanercept was more effective than dexamethasone for leg and lower back pain due to spinal stenosis.[101] Therefore the evidence is mixed for this therapy.

Previously, both human and animal data suggested that epidural local anesthetic may be similar to CSs in analgesic effect.[102–110] In 2008, Manchikanti and colleagues[102] performed a double-blind RCT comparing LA alone with LA and non-particulate betamethasone in fluoroscopically guided cervical IL-ESI. More than 70% of patients in both groups reported pain relief, and there was no difference in pain relief or functional status between the groups. An RCT in patients with unilateral leg pain due to nerve root compression evaluated TF-ESIs with either 40 mg methylprednisolone, bupivacaine, or LA alone and showed no difference in any outcome measure at three months.[105] The similarity of steroids to LA injection was confirmed by Manchikanti et al. who showed that epidurally administered bupivacaine with steroids or alone are both effective modalities in treating LBP and lower extremity pain.[108]

In a study evaluating alternatives to CSs, Burgher et al.[111] studied the differences between clonidine and triamcinolone (CS) in TF-ESIs for acute lumbosacral radiculopathy. While no differences were seen between groups in pain intensity at one month, both groups showed significant improvement in pain scores at two weeks and one month compared to baseline ($P < 0.05$). The CS group showed more functional improvement at one month compared to the clonidine group ($P = 0.022$). Although adverse effects occurred, none resulted in serious complications.

Evidence-Based Medicine for Corticosteroid Epidural Injections

Several well-designed studies have corroborated the short-term benefit of ESIs.[24,26,112–114] Given the favorable natural history of most patients with radicular pain, especially those related to a disc protrusion, a thorough understanding of the benefits and risks associated with ESIs for radicular pain syndrome is needed.[13,14,16] Head-to-head studies are necessary to compare interlaminar, transforaminal, and caudal approaches to the epidural space, which may be relevant given the unique risks to the patient of each approach. A selection of these studies concerning interlaminar, transforaminal, and caudal ESIs is reviewed in this section (Tables 62.2–62.5).

In response to a systematic review by Koes et al.,[22] Karppinen and colleagues[115] hypothesized that the poor efficacy reported in ESIs might result from insufficient penetration of CS into the locus of nerve root irritation when administered via an IL-ESI. They conducted an RCT in patients with radicular pain to test the efficacy of a single TFESI (80 mg methylprednisolone with bupivacaine 5 mg/mL, 2–3 mL) compared with a 0.9% saline injection. Leg pain was significantly better in the methylprednisolone bupivacaine group at two weeks, with a 45% reduction in pain versus 24% in saline ($P < 0.01$). Back pain was better in the methylprednisolone bupivacaine group at three months; back and leg pain was better in the saline group at six months, and no difference was noted at one year. Carette and colleagues[116] performed an RCT of lumbar IL-ESIs with either methylprednisolone or saline in patients with lumbar radiculopathy and signs of nerve root irritation or compression. The ESIs were not fluoroscopically guided, which may have led to a high frequency of misplaced injections.[39] The study did not show a statistically significant change in functional improvement as assessed by the Oswestry Disability Index (ODI), but it did find a reduction in leg pain at six weeks in the

treatment group. In a similar study, Arden and colleagues[24] performed an RCT to examine the efficacy of lumbar IL-ESIs with either 80 mg of triamcinolone and 10 mL of 0.25% bupivacaine or a placebo group of normal saline in 228 patients with unilateral lower extremity pain and signs of nerve root irritation (Table 65.2). The treatment group showed significant improvement in self-reported function and 75% improvement in ODI at three weeks. No statistically significant differences existed between the groups at six weeks or beyond in any outcome measure.

Bush and Hillier[112] performed an RCT of caudal ESIs without fluoroscopic guidance in patients with intractable radicular pain, signs of lumbar nerve root irritation, and a positive straight leg raise test. The treatment group received 25 mL (80 mg triamcinolone and 0.5% procaine), and the placebo group received 25 mL of saline. The treatment group showed a statistically significant improvement in lifestyle and pain reduction at four weeks ($P = 0.02$). At one year, both groups showed statistically significant resolution of their symptoms, further demonstrating the positive natural history of radicular pain.

The different technical approaches to the epidural space also complicate studies due to variable efficacy and risks. The efficacy of the transforaminal approach versus the interlaminar approach is not well-established; one study showed that the two approaches are similar in terms of pain relief and functional capacity.[59] Lipetz and colleagues proposed that after TFESI for lumbar radiculopathy, only one-third of patients experienced significant and long-lasting pain relief after the first injection (Table 65.3).[117] According to an RCT by Makkar et al. on patients with unilateral

TABLE 65.2 Selected Studies—Interlaminar Epidural Steroid Injections

Authors	Patients	Design/Technique	Outcome Measure	Conclusion
Arden, et al.[24]	C = 108 T = 120	RA, DB, PC No fluoroscopic guidance	1- Oswestry 2- VAS, others	Improvement at three weeks with ESI but not after that
Wilson-MacDonald, et al.[25]	C = 48 T = 44	RA, DB, PC No fluoroscopic guidance	Oswestry Oxford pain chart	Improvement at 35 days with ESI but not after that
Carette, et al.[116]	C = 80 T = 78	RA, DB, PC No fluoroscopic guidance	Oswestry VAS, others	Improvement in leg pain at six weeks but not after that
Rados, et al.[59]	IL=31 TF=32	RA, PC, fluoroscopic guidance	1- VAS 2- Oswestry	No difference between IL and TF injections, both improved after 24 weeks
Sencan, et al.[119]	IL=34 TF=33	RA, DB, fluoroscopic guidance, one injection	NRS Oswestry 3- Beck depression inventory Pain free walking distance	IL and TF are reliable treatment options. Both improved at all follow ups (three weeks, three, six months)
Do, et al.[120]	IL=60	PO, fluoroscopic guidance, moderate vs. severe lumbar central spinal stenosis	NRS	Il may be effective for moderate or severe lumbar central spinal stenosis but is limited, especially for patients with severe symptoms
Jang, et al.[123]	Ultrasound guided nerve root block=44 IL=41 TF=37	R, RA, fluoroscopy guided IL and TF	Neck disability index score Visual numeric scale	All groups have pain relief at all follow ups (one, three, six months). Ultrasound guided nerve root block is recommended for patients with lower cervical radicular pain due to low intravascular injection rate
Sabbaghan, et al.[118]	IL=111	R, fluoroscopic guidance, one injection	VAS Oswestry	Triamcinolone epidural injection with a translaminar approach is effective for spinal canal stenosis
Sencan, et al.[140]	C=61	PO, fluoroscopic guidance, one injection	NRS	Improvement at all follow ups with ESI. Severe foraminal stenosis and high spinal lever cervical disc herniation can negatively affect treatment outcomes

C, Cervical; *DB*, double-blind; *ESI*, epidural steroid injection; *R*, retrospective; *PO*, prospective observational; *PC*, prospective controlled; *RA*, randomized; *T*, thoracic; *VAS*, visual analog scale; *NRS*, numeric rating scale; *IL*, interlaminar; *TF*, transforaminal.

lumbar radiculopathy, the TFESI and para-sagittal interlaminar approaches are equivalent and superior to midline interlaminar in terms of effective pain relief and a decrease in disability; they are supported by significantly better pain relief at six months, as assessed by visual analog scale (VAS) and ODI scores.[58] TFESI is a potentially efficacious treatment for patients with spinal canal stenosis,[118] and lumbar spinal stenosis,[114] but the risk of arterial injury is increased compared with other approaches. Sencan et al. postulated that the interlaminar approach might be preferred due to the ease of the procedure, while the transforaminal approach may be preferred for patients with predominantly neuropathic pain.[119] Other studies suggest better efficacy of the transforaminal approach over the interlaminar approach when the radicular pain is limited to one nerve root.[57] The interlaminar approach may also palliate pain from lumbar central spinal stenosis, but the effect is limited, especially in severe stenosis.[120] Any patient with severe canal stenosis is not a candidate for IL-ESI due to lack of posterior epidural space and risk of cord injury. Therefore approaches are limited to transforaminal or caudal in these patients. Patients with prior spine instrumentation are not candidates for IL-ESI due to scarring of the epidural space. Therefore approaches are limited to transforaminal or caudal in these patients as well.

In part due to the inability to use the IL-ESI approach after posterior neuraxial surgery, other methods of steroid administration have been evaluated and compared to fluoroscopic ESIs. A 2020 retrospective study by Bureau and colleagues examined computed tomography (CT)-guided injectate dispersal patterns and therapeutic efficacy of cervical TFESI versus intraarticular facet steroid injection. They concluded that steroids injected into the extraforaminal or juxta-articular facet space had a better safety profile and were more efficacious than cervical TFESI.[121] Dashfield and colleagues[122] performed an RCT comparing caudal ESI with targeted steroid placement during spinal endoscopy for chronic sciatica (Table 65.4). Each group received 10 mL of 1% lidocaine with 40 mg triamcinolone. The results showed a significant benefit in patient outcomes for both groups, but no significant difference between the groups. Jang et al.[123] studied ultrasound guided selective nerve root block (US-SNRB) versus fluoroscopically guided IL-ESI and TFESI for radicular pain in the lower cervical spine. According to the Numeric Rating Scale and the Neck Disability Index, significant improvements in pain were found in all groups at one, three, and six months. The study suggests that US-SNRB should be considered as an approach for therapeutic ESI. Bahar-Ozdemir conducted a prospective observational study to determine whether the current psychiatric condition of the patient can affect the results of lumbar TFESI. The study concluded that psychiatric conditions could negatively affect the pain and disability of patients

TABLE 65.3 Selected Studies—Transforaminal Epidural Steroid Injections

Authors	Patients	Design/Technique	Outcome Measure	Conclusion
Karppinen, et al.[115]	C = 80 T = 80	RA, DB, PC Fluoroscopic guidance, one injection	VAS Oswestry, others	Improved leg pain at two weeks, no difference at four weeks. Increased back and leg pain at six months in the CS group
Riew, et al. (both RCT and five year follow up data)[129,133]	C = 27 T = 28	RA, DB, PC Fluoroscopic guidance, up to four injections	Rate of operative intervention	Reduced surgical rates in the group receiving CS + LA
Lipetz, et al.[117]	TF=94	R, fluoroscopic guidance, up to two injections	Custom Pain Survey, zero to five	One-third of patients had significant pain relief with a single injection, two-thirds of patients had significant pain relief with a second injection
Makkar, et al.[58]	Midline IL=21 Parasagittal IL=20 TF=20	RCT, DB, no control, fluoroscopic guidance, one injection	VAS 2- Oswestry	Improved pain relief at six months in Parasagittal IL and TF groups
Jang, Chang[114]	TF=54	R, fluoroscopic guidance, patients with lumbar spinal stenosis	NRS Repetitive TF epidural injections	TF is a safe modality for controlling radicular pain following lumbar spinal stenosis
Bahar-Osdemir, et al.[124]	TF=103	PO, effects of comorbid psychiatric conditions on TF outcomes	NRS Oswestry Hospital Anxiety and Depression scale	Treatment methods should not change based on psychiatric comorbidities
Vallée, et al.[138]	TF=32	PO, fluoroscopic guidance	VAS	Improvement at three weeks with ESI. No change in improvement at six months

C, Cervical; *DB*, double-blind; *CS*, corticosteroid; *LA*, local anesthetic; *R*, retrospective; *PO*, prospective observational; *PC*, prospective controlled; *RA*, randomized; *RCT*, randomized controlled trial; *T*, thoracic; *VAS*, visual analog scale; *IL*, interlaminar; *TF*, transforaminal.

TABLE 65.4 Selected Studies—Caudal Epidural Steroid Injections

Authors	Patients	Design/Technique	Outcome Measure	Conclusion
Bush and Hillier[112]	C = 11 T = 12	RA, DB, PC No fluoroscopic guidance	VAS Grogono and Woodgate Symptomatology Questionnaire	Improved leg pain and lifestyle at four weeks, no significant difference at one year
Dashfield, et al.[122]	Caudal = 33 Endoscopy = 27	RA, DB Caudal ESI versus targeted endoscopic delivery of steroid fluoroscopy used	McGill Pain Questionnaire Hospital Anxiety and Depression Scale VAS	Reduction in pain intensity and anxiety in the caudal group at six weeks, three months, and six months

C, Cervical; *DB*, double-blind; *ESI*, epidural steroid injection; *PC*, prospective controlled; *RA*, randomized; *T*, thoracic; *VAS*, visual analog scale.

before and after ESI, but these patients should still be offered interventional treatment.[124]

The efficacy of surgical procedures for many spinal conditions has come under scrutiny largely because of disparate geographic practice patterns, inconsistent outcomes,[14] and cost-benefit analyses. Patients widely accept the surgical treatment of acute radiculopathy, but studies comparing surgery with comprehensive nonsurgical care usually reveal equivocal findings, with some favoring non-operative care,[125] some stating that operative treatment is effective,[11,12,16,126] and most studies demonstrating clinically similar outcomes between groups given the favorable natural history of radicular pain (Table 65.5).[13,14,16]

Short-term outcome data from the Comprehensive Spine Pain Outcomes Research Trial (SPORT) regarding nonsurgical versus surgical care of lumbar disc herniation[13] demonstrated no statistically significant superiority of surgical discectomy over conservative care. Thus the use of conservative treatments, including ESIs, will likely continue to increase (Fig. 65.9A–C). However, in a systematic review of the 10 year outcomes of SPORT, results of the four and eight year as-treated analyses showed significantly greater improvements in patients treated surgically.[126] Unfortunately, the long-term outcomes of lumbar disc herniation are challenging to treat, regardless of approach.[114] In addition, SPORT agreed with previous trials[11,15,126] that the natural history of discogenic radicular pain consists of slow improvement over time. Outcomes of patients undergoing surgical versus nonsurgical treatments for lumbar spinal stenosis continue to be similar in terms of decreased pain burden and change in functional status, but complication rates increase with surgical management.[127] When surgical options are unavailable, ESI can be an effective treatment.[128] Follow up data from a controlled trial of lumbar TF-ESIs suggest that non-operative care may be effective in decreasing the need for disc surgery over time, with lower morbidity.[129] Findings from epidemiologic studies of cervical radicular pain demonstrate similar results.[130,131]

A study of 192,777 patients who received CESI for radiculopathy, cervical disc herniation, or stenosis found that within five years, one in five patients underwent surgery.[132] Patients with stenosis or disc herniation were more likely to have surgery than patients with isolated radiculopathy. Patients with repeated injections were less likely to continue surgery,[132] which is consistent with a study by Riew et al. who found a significant reduction in the frequency of lumbar spine surgery in patients treated with up to four TF-ESIs.[133] In follow up data, Riew[129] discovered that patients in the bupivacaine-betamethasone group versus the bupivacaine-only group had no significant differences in avoiding operative treatment. However, Gerling et al.[113] found that ESIs did not have a surgical-sparing effect for patients with degenerative spondylolisthesis, again demonstrating the importance of patient selection for intervention.

There are known predictors of eventual operative management, such as male sex and prior opioid use,[125] and there is also a likely association between biomarkers and response to ESI. Schaaf proposed that 35% of pain patients were responders, which correlated with baseline plasma levels of certain substances, namely, lower levels of chondroitin sulfate-846 and higher neuropeptide Y and serotonin levels as compared with non-responders.[134] Patients have a higher risk of requiring reoperation if a microdiscectomy is completed within the six weeks following lumbar ESI.[135] Therefore it is important for pain providers to communicate their plan for intervention if a surgery is being considered. More research is needed to assess and validate the predictive ability of patient attributes, as this is crucial for selecting surgical candidates.

Patients show clinical improvement after both interlaminar CESIs[136] and cervical TF-ESIs.[137,138] Therefore the selection of approach is at the discretion of the individual provider. Few randomized, placebo-controlled studies of CESIs, interlaminar or transforaminal, have been conducted to date.[61] One 2019 study comparing interlaminar and transforaminal approaches for cervical radicular pain showed no difference in efficacy.[139] Another study noted decreased efficacy of cervical IL-ESI treatment in patients with severe foraminal stenosis or high spinal level cervical disc herniation.[140] The latter is logically valid given that cervical IL-ESI is not typically superior to the C7-T1 interspace. However, larger studies with longer follow up periods are still needed, especially given the differing complication rates of the two approaches.

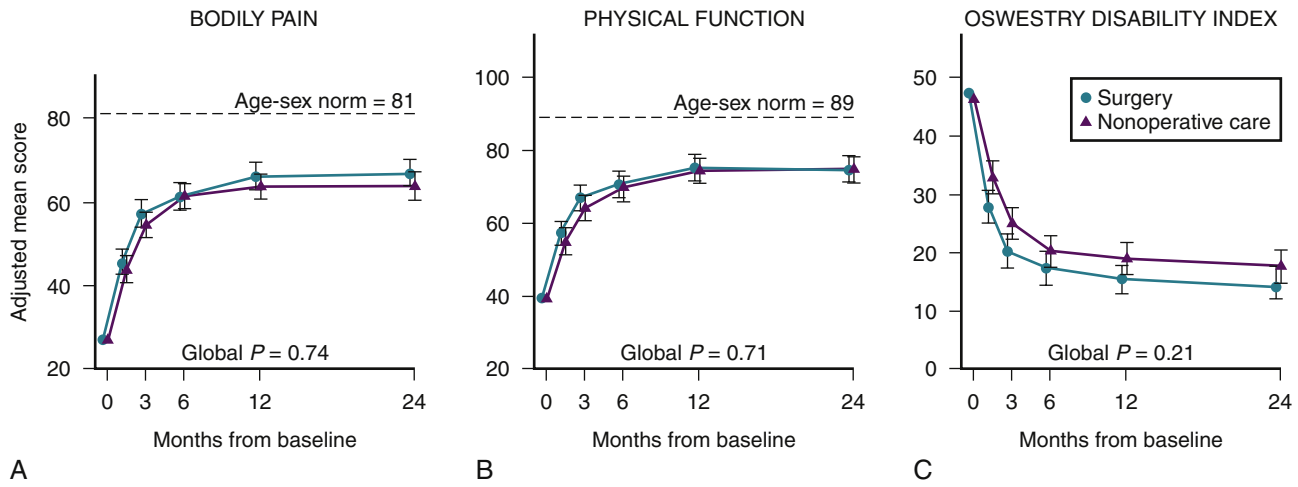
Contrast Media Use in Epidural Steroid Injections

Contrast media (CM) is employed in interventional pain procedures to confirm the correct placement of the needle tip and the absence of intravascular uptake. In most instances, the volume

TABLE 65.5 Selected Studies: Surgical vs Non-operative Treatment

Authors	Patients	Design/Technique	Outcome Measure	Conclusion
Weinstein, et al.[13]	S = 245 N = 256	RA, assigned to surgery or non-operative care	Rate of operative intervention	Both surgical and non-operative groups improved over two years
Karademir, et al.[16]	ESI = 70	R, review of patients with symptomatic lumbar intervertebral disc herniation	VAS Oswestry 3- Modified Ashworth Scale	Surgical treatment recommended for patients with persistent low back pain for more than six weeks
Atlas, et al.[11]	S = 217 N = 183	PO, ten year outcomes of patients with lumbar disc herniation	Rate of operative intervention	Surgically treated patients have more complete relief after ten years. Improvements were similar regardless of treatment
Oster, et al.[126]	54 articles reviewed in full	Meta-analysis, ten years clinical outcomes of Spine Patient Outcomes Research Trial	Short Form-36 Health Status Questionnaire 2- Oswestry	Surgical treatment was greater at three months and two years compared to non-operative treatment in the observational cohort. No difference in the RCT cohort. Surgically treated patients had greater improvements at four and eight years
McCormick, et al.[15]	Percutaneous lumbar disc decompression = 70 One year follow up = 40 Eight year follow up = 25	PO, patients with discogenic lumbosacral radicular pain	NRS Oswestry Rate of operative Intervention	Percutaneous lumbar disc decompression has relief over long-term follow up
Zaina, et al.[127]	26 articles reviewed in full	Meta-analysis, surgical vs. non-operative treatment in patients with lumbar spinal stenosis	Oswestry Zurich Claudication Questionnaire	Surgical vs. non-operative approach was similar in treating lumbar spinal stenosis. Surgical treatment includes side effects not reported in non-operative management
Gomes, et al.[128]	ESI = 32	PO, dogs with degenerative lumbosacral stenosis	Rate of operative intervention	Surgical decompression can lead to a more favorable outcome. ESI is a long-term alternative treatment
Kleimeyer, et al.[132]	192,777	R, C, ESI for diagnoses of cervical disc herniation or stenosis, or radiculopathy	Time of ESI to surgery	Over one-fifth of patients continued to surgery in five years. Patients with repeat injections are at a lower risk to continue to surgery
Gerling[113]	Control = 192 Epidural injection = 74	R, surgical candidates with degenerate spondylolisthesis	Short Form-36 Bodily Pain score Self-reported preference for surgery	No relationship between ESI and improved clinical outcomes over a four year period
Lilly, et al.[125]	277,941	R, patients with lumbar intervertebral disc herniations	Rate of operative intervention	Non-operative treatment can be used successfully for the majority of patients. Predictors of treatment failure include male sex and prior opioid use
Bhattacharjee, et al.[135]	12,786	R, microdiscectomy patients	Rate of operative intervention	Six month reoperation rates increase with patients who received injections six weeks prior to surgery
Bush, Hillier[137]	68	PO, serial periradicular/ epidural corticosteroid injections	Rate of operative intervention	All patients had relief without surgery at an average of 39 months

S, Surgery; *N*, non-operative; *DB*, double-blind; *LA*, local anesthetic; *R*, retrospective; *PO*, prospective observational; *PC*, prospective controlled; *RA*, randomized; *RCT*, randomized controlled trial; *VAS*, visual analog scale; *ESI*, epidural steroid injection.



• **Figure 65.9** Data from the Spine Pain Outcomes Research Trial demonstrate no significant difference between bodily pain scores (**A**), physical function (**B**), and Oswestry Disability Index (**C**) over a two month study period in which surgery was compared to conservative care of patients with radicular pain. (Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs. nonoperative treatment for lumbar disc herniation: the spine patient outcomes research trial (SPORT): a randomized trial. *JAMA*. 2006;296:2441–2450.)

injected is 1–3 mL and may be repeated. Overall, CM should be used in ESI procedures. Cervical and lumbar IL-ESIs should be performed using image guidance and a test dose of CM. Additionally, dye injection to evaluate needle placement of cervical and lumbar TFESI should be conducted with real-time fluoroscopy.[141]

Several developments have impacted the continued use of radiocontrast agents for ESIs. These include gadolinium (Gd) deposition/retention in the brain following repeated administration of gadolinium-based contrast agents (GBCAs),[142–144] and encephalopathy from unintentional intrathecal injection of GBCA.[145,146] Another concern with CM for interventional procedures relates to hypersensitivity reactions (HRs) and iodinated contrast medium (ICM).[147] See more on contrast agents in Chapter 73.

High signal intensities in the dentate nucleus and globus pallidus in patients exposed to linear GBCAs were first reported by Kanda et al.[142] They noted that the dentate nucleus-to-pons and globus pallidus-to-thalamus signal intensity ratios in patients who had undergone contrast-enhanced examinations were significantly greater than those who underwent unenhanced examinations. Other investigators have also demonstrated the deposition of Gd in the skin and bones of patients exposed to CM.[148,149] However, brain deposition/retention in this instance pales in comparison to catastrophic sequela from unintentional IT gadolinium injection. Factors to consider when choosing a specific GBCA include diagnostic efficacy, rate of adverse reactions, dosing and concentration, radio-opacity, and the propensity to deposit in organs such as the brain. While gadobutrol has the highest radiographic conspicuity (pixel value difference with respect to background), it contains the highest molar concentration of Gd.[150] This increased concentration likely increases the risk of encephalopathy after unintentional IT Gd injection. More research is needed to determine the clinical significance of gadolinium brain deposition after small extravascular injections, typical of interventional pain procedures.

Cases of encephalopathy after unintentional IT injection of gadolinium have been reported after interventional pain procedures.[30,146,151,152] The risk of unintentional IT injection after an IL-ESI is well known (0.2%) but also occurs with TF-ESIs (0.04%).[153] In one report, seizures, impaired consciousness, and intubation resulted from gadobutrol (1.5 mL) unintentionally injected into the intrathecal space prior to an ESI.[146] Another patient developed pain and spasms in the lower extremities after injection of 2 mL gadobutrol for an IT catheter contrast study.[152] Both patients fully recovered. However, a 2019 publication reported a patient who required intubation within 12 h of unintentional intrathecal gadoteridol injection during the minimally invasive lumbar decompression procedure. The patient died 18 days later.[30] Encephalopathy after unintentional Gd injection is of grave concern to the interventional pain physician given the potentially catastrophic sequelae.

Of the iodinated CM, iohexol and iopamidol are FDA-approved for intrathecal use and are used for spine interventional pain procedures. In the absence of HRs to ICM, these agents provide an alternative when interventional pain procedures with a high risk of IT injection are performed in the spine.

Immediate contrast reactions can be non-immunoglobulin E (IgE)-mediated or IgE-mediated. The pathways of non-IgE-mediated reactions include a direct membrane effect on the basophil or mast cell, complement activation, or bradykinin generation.[154] Most HRs to CM are anaphylactoid in nature, also called idiosyncratic or non-allergic hypersensitivity.[155,156] The American College of Radiology classified the reactions as allergic-like and physiologic in nature and the severity of reactions from mild to moderate to severe.[157] The greatest risk factor for HR to CM is a previous history of HR, but other predisposing factors include asthma, atopy, severe cardiovascular disease, female sex, and drug allergy.[158,159]

Clinical trials show the overall and severe adverse reaction rates to low osmolar ICM to be 0.2%–0.7% and 0.01%–0.02%, respectively.[160–162] The incidence of HR is higher with ICM than with Gd. A review and meta-analysis of nine trials (716,

978 administrations) showed that the overall and severe rates of allergic-like reactions were 9.2 (0.092%) and 0.52 (0.0053%) per 10,000 administrations, respectively.[163] Similar to ICMs, HRs-to-GBCAs are mostly mild in nature. The most frequent allergic-like symptoms are urticaria and respiratory or throat symptoms.[164] The risk factors are the same as those for ICM: previous HR (recurrence rate 30%), female sex, allergies or asthma, number of exposures, inpatient status, and imaging target (abdomen and/or pelvis).[159,164–166] In terms of structure, HRs are more common with macrocyclic GBCAs than with linear GBCAs, partly because of their higher osmolality.[156] Macrocyclic GBCAs may also be used in patients who have had moderate or severe HRs to ICM, and linear GBCAs are also an option for spinal injections. Regardless of the gadolinium agent employed, caution should be exercised to avoid unintentional injection of Gd into the IT space.

In a case series, six patients with a history of previous HR to intravenous ICM for diagnostic procedures did not have breakthrough reactions when ICM was injected into the epidural space without pretreatment. Patients had a history of HR to ICM and were given iodinated contrast during an interventional pain procedure. Regardless of patient history in reaction to high volume contrast from prior CT, the authors ascribed the lack of breakthrough reactions during ESIs to the small (1–3 mL) volumes of CM injected, slow absorption from the epidural space, and concurrent administration of steroids.[147] Patients should be observed for at least 30 min after the procedure, especially in patients with a history of HRs. For patients with mild reactions, physicians may determine if pretreatment of these patients is necessary. While most interventional pain radiologists do not pretreat, anesthesiologists often opt for pretreatment. In cases of mild reactions, the use of steroids for pretreatment should be a risk-benefit analysis based on the patient's comorbidities. This is based on the assumption that ICM has been elected because GBCA use is contraindicated for the procedure (i.e. interlaminar epidural injection).

Complications of Epidural Steroid Injections

Complications of ESIs can be ascribed to the procedure or injection. Complications from the procedure include neurologic injury, infection, and bleeding/hematoma. Complications from the injectate include neurologic injury and systemic side effects.[167] A 2004 closed claims study revealed that ESIs accounted for 40% of all chronic pain management claims. Of the 114 ESI claims in the study, 25% were nerve injuries, 21% infections, 18% headaches, and 8% were deaths or brain damage.[168] The nerve injuries resulted in paraplegia or quadriplegia, either from injection into the spinal cord or compression due to epidural abscess or hematoma. Infections included meningitis and epidural abscesses. Death or brain damage occurred only in ESIs involving administration (achieved or attempted) of LA to the epidural space and, in some cases, with co-administration of opioids.

A follow up publication from the Closed Claims group noted that cervical procedures accounted for 22% (64/294) of chronic pain treatment claims, the most common being needle trauma to the spinal cord, neural ischemia after intra-arterial injection, and dural puncture.[169,170] Spinal cord damage was noted in 59% of patients, with direct needle trauma as the leading cause (31%). In 67% of cervical intervention claims, general anesthesia or sedation was employed compared to 19% of claims without spinal cord injuries. In patients with spinal cord injuries, 25% were unresponsive during the procedure compared to 5% of patients with cervical interventions but did not have spinal cord injury. Appropriate sedation allays anxiety and reduces the risk of sudden movement but still allows reporting of pain or paresthesia when there is needle-to-nerve contact. In contrast, heavy sedation eliminates the patient's ability to communicate warning signs of cord injury and is not recommended during neuraxial procedures.[170] Back pain after lumbar spine intervention is usually mild, localized, and resolves within two to three days. Back pain is attributed to tears in the ligaments, fascia, or bone with localized bleeding, immobility of the spine, relaxation of the paraspinal muscles under anesthesia, flattening of the normal lumbar convexity, and stretching and straining of the lumbosacral ligaments and joint capsules.[171] Other findings of the Closed Claims group included the use of radiographic guidance in 76% of claims and the use of contrast in 57% of claims with spinal cord injury. After reviewing the records for each case, the reviewers concluded that the appropriate use of radiographic guidance would have prevented spinal cord injury in 45% of claims with injury compared to 17% of claims without injury.[169]

A more recent analysis of malpractice claims regarding outpatient interventional pain procedures involved the Controlled Risk Insurance Company.[172] The analysis identified 126 closed claims, of which 34 were lumbar and 31 were cervical IL-ESIs. The common alleged events included improper performance of the procedure (n = 38), nonsterile technique (n = 17), unintentional dural puncture (n = 13), and needle misdirected to the spinal cord (n = 11). The commonly reported outcomes included worsening pain (n = 26), spinal cord infarct (n = 16), epidural hematoma (n = 9), and postdural puncture headache (n = 9). Perceived deficits in technical skills were present in 83% of claims.

Postdural Puncture Headaches

Although rare, postdural puncture headaches (PDPHs) may occur after diagnostic lumbar puncture. Benzon et al. studied the incidence of PDPHs in patients who received dural punctures and noted that 13 of 142 (9%) developed headaches. Treatment for postdural headache consists of intravenous and oral fluids, analgesics, bed rest, and, if necessary, an epidural blood patch.[173] The clinician should be alerted to the presence of intracranial pathology in patients with classic PDPH with a postural component, in which headache worsens with standing or sitting and improves in the supine position and is accompanied by typically associated signs and symptoms such as nausea, vomiting, and neck stiffness.[174]

Vascular Injury

Intraarticular C1-C2 (lateral atlantoaxial joint) injections are now uncommon because of reports of stroke due to injection of the vertebral artery.[175] Several cases of CNS injuries involving the brain or spinal cord have been described after TF-ESIs. Events involving the brain consist of cerebellar infarction, cortical blindness from edema of the occipital cortex, or death from brain stem hemorrhage.[176–178] These events have been ascribed to embolism of particulate steroid, trauma to the vertebral artery, or vasospasm from the injected contrast or steroid. Spinal cord events included paraplegia or quadriplegia.[179–184] Cases involving particulate steroids were permanent, while non-particulate injectates (CM or LA) caused temporary events (lower extremity paralysis or blindness for three weeks).[179,184] One case of permanent injury after

use of non-particulate steroid was attributed to either vasospasm from the needle tip or injectate and/or anterior spinal artery obstruction from a thrombus formation, intimal flap formation, or dissection.[183] Kim et al. found that approximately 30% of transforaminal injections demonstrated intravascular spreading patterns during real-time fluoroscopy, which was significantly more likely in the cervical than the lumbar spine ($P < 0.001$). The authors suggest using at least 3 mL of contrast agent during neurogram to ensure that the needle tip is outside the vasculature.[185]

Regarding particle size, methylprednisolone acetate and compounded betamethasone preparations were noted to be the largest size, triamcinolone acetonide was intermediate, and betamethasone sodium phosphate/betamethasone acetate was the smallest.[176,186] If a non-soluble steroid is preferred, the recommended preparation is commercial betamethasone. Commercially available betamethasone (Celestone Soluspan^{R}) contains 3 mg/mL betamethasone sodium phosphate, which is non-particulate and short-acting, and 3 mg/mL betamethasone acetate, which is long-acting and particulate.[186] Dexamethasone was noted to be purely non-particulate in one study[176] and to contain small particles in another study.[186] In addition, the particles were noted to aggregate very quickly. These particles are large enough to occlude possible vascular routes of embolism. Studies investigating the routine use of dexamethasone are needed to determine its safety and efficacy.

For cervical TF-ESIs, the routes of embolization of the particulate steroid include the vertebral artery, ascending cervical artery, deep cervical artery, and the radicular artery accompanying the nerve root.[62,186–188] For lumbar TF-ESIs, the routes include the radicular artery, a low-lying artery of Adamkiewicz, or in rare cases, the Desproges-Gotteron artery. The artery of Adamkiewicz is in the upper half of the foramen 97% of the time and has never been observed in the most inferior fifth of the foramen[187] and may be present at any level of the lumbar spine, although more common at high lumbar levels (Fig. 65.10). Similarly, the Desproges-Gotteron artery may be present in the Kambin triangle, even at the L5 vertebral level. It may explain the rare instances of paralysis that have been reported at low lumbar levels. A cadaver study revealed that the ascending cervical and deep cervical arteries supply medullary arteries to the anterior spinal artery and that the ascending cervical and deep cervical arteries anastomose with the vertebral artery.[62] Also noted was the close proximity—within 2 mm of the needle tip—of the ascending cervical and deep cervical arteries to the cervical SAP, which is a landmark for cervical TF-ESIs, as referenced earlier in the chapter (Fig. 65.1). An ultrasound study confirmed the presence of many vessels at or in the projected pathway of selective nerve root blocks at C5–C7.[188] These findings explain reported embolisms to the brain or segmental infarct of the spinal cord from TF-ESIs. The contrast or particulate steroid can be injected into the radicular artery, which connects to the anterior spinal artery. The injection of methylprednisolone into the vertebral artery of pigs resulted in the animals becoming unconscious and requiring ventilator support, whereas animals that received dexamethasone showed no evidence of injury.[189] In another study the injection of different steroids into the carotid artery of rats, resulted in cerebral hemorrhage with the following incidences: eight of 11 for methylprednisolone, zero of eight for dexamethasone and saline, and three of six for the carrier.[190] The findings for the carrier may be attributed to a reaction to the preservative. Although rare, it is still possible for vascular injury to occur even with the use of a water-soluble steroid such as dexamethasone.[183]

Solvent Toxicity

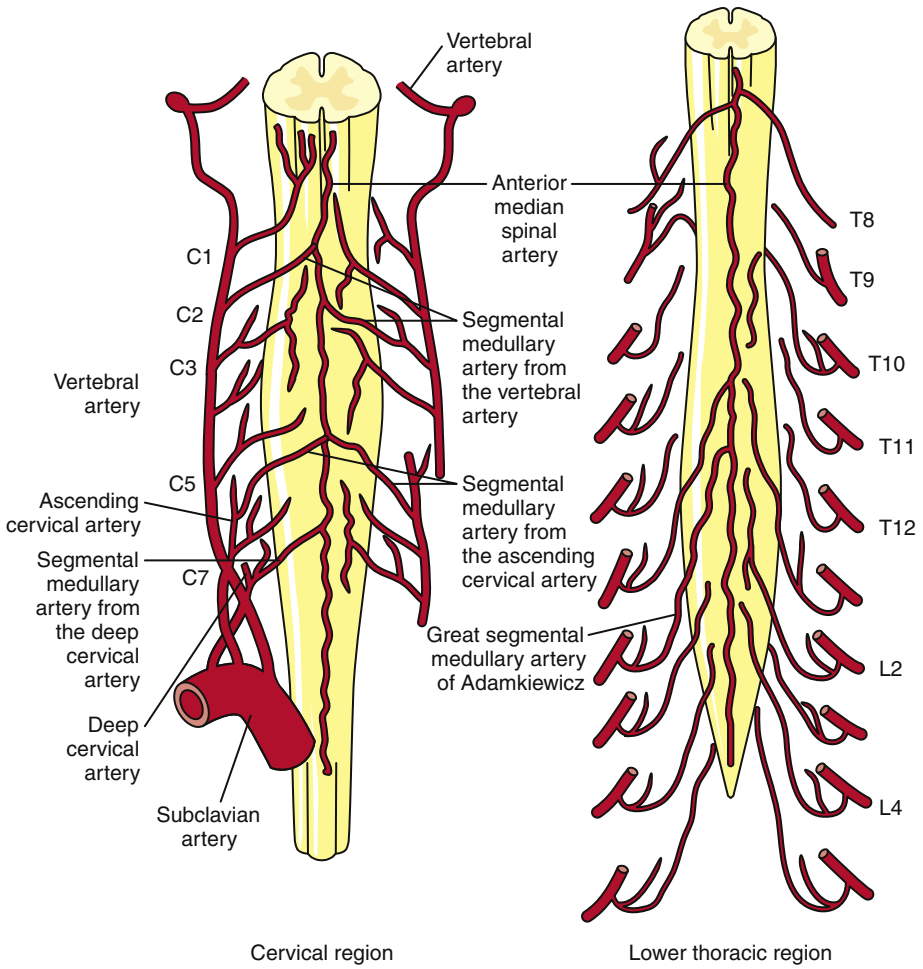
Steroids contain a vehicle and preservatives to prolong their shelf life. These include benzyl alcohol, polyethylene glycol, myristyl γ-picolinium chloride (MGPC), and benzalkonium chloride (BKC).[191] The neurotoxicity of benzyl alcohol was deduced after a primigravida developed flaccid paralysis after unintentional subarachnoid injection of 40 mL of 0.9% NaCl containing 1.5% benzyl alcohol. The patient recovered after 30 h and had complete recovery after six months.[192] In contrast, no motor block was noted after injection of 40 mL of 2.5% benzyl alcohol into the caudal space of a patient with pelvic cancer pain.[193] Animal studies also showed no neurotoxicity from benzyl alcohol. Regarding polyethylene glycol (PEG), in an isolated nerve preparation, 30% PEG decreased the amplitudes of the compound action potentials of the A, B, and C-fibers, while 40% abolished the potentials.[194] Concentrations greater than 40% could not be studied because of their viscosity. All compound action potentials recovered within a 2 h washout. Intravitreal injection of 1 mL of 0.38, 0.76, or 1.52 mg/mL MGPC resulted in disarrayed and swollen fibers in the retina of rabbits 24 h after injection. Loss of retinal layers occurred at six weeks.[195] The conjunctival application of BKC resulted in a 30% decrease in stromal nerve fiber density with a 0.01% concentration and 60% decrease with 0.1%.[196] It should be noted that the concentrations of the vehicles and preservatives used in these studies, other than BKC, were several-fold higher than their concentrations in the commercial depot steroid preparations.[191] The collective data on animal studies exonerate the preservatives in the commercial depot steroids as being neurotoxic when injected into the epidural space.[197–199] Additionally, the steroid is typically diluted with 1–3 mL saline or LA before ESI, further decreasing concentrations of the preservatives. Concerns regarding adverse events due to preservatives prompted clinicians to order compounded steroids without any vehicle or preservatives. However, the use of contaminated compounded steroids led to multistate cases of fungal meningitis.

Injectate Contamination

Clinicians who use compounded steroids often sense that they avoid neurotoxicity from the preservatives and that they are cheaper than commercial depot steroids. However, compounded steroids pose practical issues. For example, a New England company's production of a contaminated compounded steroid led to a multistate outbreak of fungal infections.[200] This devastating event led to increased federal supervision of compounding companies. In 2012, more than 590 cases of fungal meningitis were reported after ESI of contaminated compounded methylprednisolone. In response to these adverse events, the Pharmacy Compounding Accreditation Board (PCAB) was created to evaluate compounding companies and hold them accountable to nationally accepted quality control, quality assurance, and quality improvement standards. That year, only 2% of compounding companies participated in the PCAB program. PCAB accreditation will ensure the preparation of sterile and safe medication, but further legislative and regulatory changes are needed to prevent future adverse events.[191]

Epidural Abscess

This is a rare complication of ESIs. A study showed no infection after 4265 epidural injections in 1857 patients over a seven year period.[201] However, infections after ESIs have been reported, and

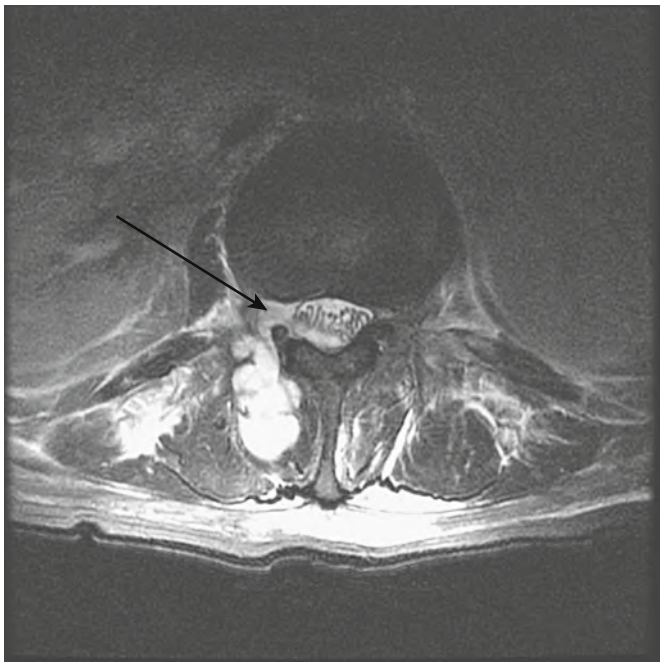


• **Figure 65.10** Artist's adaptation of an earlier drawing from Gillilan. *Left panel*, Contributions of several segmental medullary vessels to the anterior median spinal artery; *right panel*, great segmental medullary artery of Adamkiewicz entering at the L2 intervertebral foramen on the left side. (From Gillilan LA. The arterial blood supply of the human spinal cord. *J Comp Neurol.* 1958;110:75–103.)

although suspicion is raised due to patient history and physical, the definitive diagnosis is achieved with MRI (Fig. 65.11). A retrospective review of a prospectively maintained database of 1182 cervical ESIs and 4617 lumbar ESIs revealed three cases of infection, all in the lumbar group.[202] An analysis of 128 cases of purulent meningitis showed eight cases of paraspinal abscess originating from injections, one due to an ESI, and the remaining seven due to facet or paravertebral injections.[203] Factors resulting in infection include breaks in sterile techniques, skin disinfectant failures, contaminated instruments and injectates, and hematogenous dissemination. Immunocompromised patients are at an increased risk of infection. A review of 14 cases of epidural abscess or meningitis reported in the literature revealed that eight of the 14 patients were immunocompromised. In their review the authors noted that the cultures of blood, cerebral spinal fluid, or pus in all patients were positive for *Staphylococcus aureus*.[204] In addition to immunocompromised patients' susceptibility to infection, adrenal suppression can occur from the injected steroid.[205] The American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine (ASRA) published a practice advisory on prevention, management, and diagnosis of infectious complications after neuraxial techniques.[206,207] Some of their recommendations on aseptic techniques include removal of jewelry (e.g. rings and watches), hand washing, wearing of caps, wearing masks covering both mouth and nose, sterile gloves, sterile draping of the patient, use of individual packets of antiseptics for skin preparation, use of antiseptic solutions (e.g. chlorhexidine with alcohol) for skin preparation, and allowing for adequate drying time. An expanded discussion of infections is presented in Chapter 74.

Disease-Modifying Anti-rheumatic Drug Complications

Nonbiologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) are used to slow rheumatoid arthritis disease progression. Nonbiologic DMARDs include methotrexate, sulfasalazine, hydrochloroquine, leflunomide, and doxycycline. Biologic agents include etanercept, golimumab, infliximab, abatacept, certolizumab, rituximab, tocilizumab, anakinra, secukinumab, ustekinumab, belimumab, and tofacitinib. There is an increased risk of perioperative infection in patients taking more than one DMARD.[208,209] National rheumatology associations caution that the risks of postoperative infection must be balanced against the possibility of arthritic flare from discontinuation of therapy. The guidelines advise the continuation of DMARDs, such as methotrexate, perioperatively. Biologics should be stopped before



• **Figure 65.11** An accumulation of abscess material (*arrow*) is seen tracking epidurally and into the perispinal soft tissues. (From Hooten WM, Kinney MO, Huntoon MA. Epidural abscess and meningitis after epidural corticosteroid injection. *Mayo Clin Proc.* 2004;79:682–686.)

surgery; the interval depends on the pharmacokinetics of the specific drug.[210–213] Anti-TNF drugs should not be used during the preoperative period for at least one week prior to, and one week after surgery,[209] or stopped for three to five times the half-life of the relevant drug prior to surgery.[210] Resumption is advocated when the wound is healed, usually around 14 days, and in the absence of infection. There have been no reports of infection after epidural administration in a patient taking a DMARD drug. However, there has been a case of spinal and paraspinal inflammatory reaction (mass) after ESI in a patient who was taking methotrexate, adalimumab, and prednisone.[214] Several cultures of the lesions in the paravertebral soft tissue, ligamentum flavum, and pedicle were negative for fungal, aerobic, and anaerobic organisms. This case demonstrates the adverse reaction in immunocompromised patients, even with strict observance of aseptic techniques.

Hematoma

Bleeding and spinal hematoma are the consequences of epidural injections. ASRA Pain Medicine guidelines on interventional pain procedures in patients on anticoagulants are discussed in Chapter 74. In patients at high risk for a cardiovascular event, a shared decision making process should be followed before anticoagulant discontinuation. It has been recommended that the $CHADS_2$ (C-congestive heart failure, H-hypertension, A-age >75, D-diabetes mellitus, S-stroke, or transient ischemic attack) score be determined.[215] In this scoring system, one point each was given for the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and two points for the history of stroke or TIA. A patient with a CHADS2 score of three should prompt the consideration of low-molecular-weight heparin (LMWH) bridge therapy, after discontinuation of the anticoagulant, with stoppage of LMWH 24 h before the procedure.

Endocrine Complications

The most common side effects or complications from ESIs are endocrine-related.[216,217] ESIs with triamcinolone and methylprednisolone cause reductions in cortisol levels for more than three weeks.[218] A study by Park et al. in patients receiving ESIs for six months or longer showed no incidence of Cushing's syndrome, but two patients (11.8%) developed adrenal insufficiency (AI). An unanticipated adrenal crisis due to AI would be rare but dangerous.[219] Therefore regular monitoring of adrenal function is suggested in patients who have received long-term ESIs.

ESIs can increase the blood sugar levels. In a study of diabetic patients, the investigators found significant increases in fasting blood sugar on post-procedure days one to three after 40 mg triamcinolone and on post-procedure day one after 20 mg of dexamethasone. Analgesia in both groups was similar.[220] The elevation of blood glucose after ESIs has been shown in other studies: a 75% increase in one study,[221] prolonged elevations for up to three days in another study,[222] and up to four days in another study.[220]

Abnormal vaginal bleeding after ESIs has been reported anecdotally. In a large paired observational retrospective cohort study of 8,166 ESIs, the authors noted that subjects were 2.8 times more likely to have abnormal vaginal bleeding during the post-injection period compared to the pre-injection period.[223] Additionally, bleeding prompted endometrial biopsies in 52% of cases; benign findings were noted in 100% of premenopausal women.

ESIs have been shown to affect bone mineral density. A systematic review of eight articles that studied 7,233 patients revealed an association between ESIs and decreased bone mineral density, and increased vertebral fracture risk.[224] The significant decreases were related to a cumulative methylprednisolone dose of 200 mg over one year and 400 mg over three years. The risk of osteoporosis and osteopenia was diminished in patients who were on anti-osteoporotic medication during the ESIs.

Neurologic Complications

The Multidisciplinary Working Group, a consortium of pain medicine organizations, under the auspices of the FDA-Safe Use Initiative, proposed safeguards to prevent neurologic complications after ESI (Table 65.6).[141,225] Moderate to heavy sedation is not recommended. The recommendation to perform the cervical IL-ESI at C6-C7 or C7-T1 is prompted by the wider diameter of these interspaces and the presence of gaps in the ligamentum along the higher cervical levels.[225] The use of a particulate steroid in cervical TF-ESIs is not recommended. However, it may be used in lumbar TFESI if an initial injection of a non-particulate steroid (e.g. dexamethasone) is ineffective.[141,225] Additionally, particulate steroids have a higher incidence of neurologic complications at the cervicothoracic level.[226] IL-ESIs without contrast is an option in patients with a history of moderate/severe HR (The topic of contrast is discussed in Chapter 73.). Digital subtraction imaging (DSI) was not approved by the group. Although DSI improves the detection of intravenous injection compared with negative aspiration assessment, it also increases radiation exposure and cannot distinguish between the arterial or venous spread. A case of paraplegia has also been reported, even with a reassuring DSI study.[227]

The multi-disciplinary working group recommendations were confirmed and amplified by the BENELUX (Belgium, Netherlands, Luxemburg) group.[228] They also recommended an LA test dose prior to injection, limiting the volume of injection to 4 mL, and TF-ESIs to be performed in the Bogduk "safe triangle" (upper

TABLE 65.6 Statements and Clinical Considerations of the Multispecialty Work Group to Reduce Neurologic Injuries after Transforaminal Epidural Steroid Injections

1. Cervical IL-ESIs are associated with a rare risk of catastrophic neurologic injury.
2. TF ESI using particulate steroid is associated with a rare risk of catastrophic neurovascular complications.
3. All cervical IL-ESIs should be performed using image guidance, with appropriate anteroposterior (AP), lateral, or contralateral oblique views and a test dose of contrast medium.
4. Cervical TF-ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient.[a]
5. Cervical IL-ESIs are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level.
6. No cervical IL-ESI should be undertaken, at any segmental level, without reviewing, before the procedure, prior imaging studies that show there is adequate epidural space for needle placement at the target level.
7. Particulate steroids should not be used in therapeutic cervical TF injections.
8. All lumbar IL-ESIs should be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views, and a test dose of contrast medium.
9. Lumbar TF-ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient.[a]
10. A non-particulate steroid (e.g. dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections.
11. There are situations where particulate steroids could be used in the performance of lumbar TF-ESIs.
12. Extension tubing is recommended for all TF-ESIs.
13. A face mask and sterile gloves must be worn during the procedure.
14. The ultimate choice of what approach or technique (IL vs. TF ESI) to use should be made by the treating physician by balancing the potential risks and benefits of each technique for each patient.
15. Cervical and lumbar IL-ESIs can be performed without contrast in patients with documented contraindications to the use of contrast agents (e.g. significant history of contrast allergy or anaphylactic reaction).
16. TF-ESIs can be performed without contrast in patients with documented contraindications to use. However, particulate steroids are contraindicated in these circumstances, and only preservative-free, particulate-free steroids should be used.
17. Moderate to heavy sedation is not recommended for ESIs, but if light sedation is used, the patient should remain able to communicate pain or other adverse sensations or events.

[a]An organization voted against statements four and nine; preferred that digital subtraction imaging should be mandatory before transforaminal injection of a potentially hazardous substance.

AP, Anteroposterior; *ESI*, epidural steroid injection; *IL*, interlaminar; *TF*, transforaminal.

aspect of the foramina) or the Kambin triangle. A test dose of LA, if intravascular, may result in neurologic signs and symptoms within 30–60 s, prompting redirection of the needle. A study demonstrated that patients with signs of systemic toxicity from the test injection of LA could prompt abandonment of the procedure, which suggests a protective effect of test dosing in avoiding neurologic complications.[229] Regarding the injection site, other authors recommend injecting at Kambin's triangle, that is, the inferior aspect of the foramen as this area is less vascular.[230] However, this triangle does not absolutely guarantee avoidance of vasculature, as the Desproges-Gotteron artery may be present even at low lumbar levels. Injury to this artery is a potential etiology of reported cases of paralysis using dexamethasone via the transforaminal route in the Bogduk "safe triangle." The lowest doses recommended by the BENELUX group were 40 mg methylprednisolone, 10–20 mg triamcinolone, and 10 mg dexamethasone. A major difference is the group's permission to inject non-particulate steroids transforaminally at the L3 level or lower.

Summary

The evidence seems to support the use of interlaminar, caudal, and transforaminal CS injections for radicular pain and painful radiculopathy secondary to spinal stenosis or disc pathology for short-term analgesia. Most studies suggest modest benefits for variable periods of two weeks to three months.[24,26,112–114] Recent studies suggest that particulate and non-particulate injections result in a similar duration of relief.[141] The short-term benefit of ESIs and the favorable natural history of radicular pain may be complementary factors with respect to the clinical improvement that is typically observed in patients. The impact of other conservative therapies, such as medications, exercise, physical therapy, and cognitive behavior strategies, combined with epidural CSs has not been studied in a robust fashion.

Given the waxing and waning nature of radicular symptoms, ESIs may provide prolonged functional benefits when used for exacerbations. However, ESIs are associated with complications, most of which are preventable. Pain medicine physicians should be aware of these complications, observe measures to avoid them, diagnose issues without delay, request expert consultation as necessary, and treat the patient accordingly. Identifying the origin of spine pain and instituting appropriate treatments should be performed by providers with expertise in pain management.

Key Points

- The natural history of discogenic radicular pain is favorable for conservative management.
- Randomized, placebo-controlled trials have shown short-term benefits with ESIs via multiple techniques.
- The best practice for nonsurgical radicular pain syndromes is yet to be defined; few comparative, nonsurgical trials have been conducted.

- Because of the rare but catastrophic nature of complications of interventional epidural treatments and the favorable natural history of radicular pain, safety should be a primary concern.
- Systemic side effects of ESIs include decreased bone mineral density, reduced blood cortisol levels over three weeks, and increased blood glucose levels.
- Neurologic complications occur after transforaminal epidural injections of steroids, the most common of which is vascular injury due to embolization of particulate steroids through the accompanying radicular artery, ascending cervical, and deep cervical arteries. The cervical arteries anastomose with the segmental medullary arteries and connect it with the anterior spinal artery.
- A multi-disciplinary pain working group recommended the initial use of a non-particulate steroid when transforaminal ESIs are employed for cervical radicular pain and painful radiculopathy.
- Caution is recommended when using gadolinium as the contrast agent because it is linked to nephrogenic systemic fibrosis, gadolinium deposition/retention in the brain, and encephalopathy/death from an unintentional intrathecal injection.
- Future research should investigate alternative pharmacologic agents or techniques to address the pathophysiology of radicular pain syndromes; the use of these agents via continuous or prolonged delivery is of interest.

Suggested Readings

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66 Radiofrequency Treatment

KOEN VAN BOXEM, MAARTEN VAN EERD, THIBAUT VANNESTE, XANDER ZUIDEMA, JAN VAN ZUNDERT

The use of electric current for pain management has a long history. As early as the second half of the 19th century, brain lesions were made in animals with the application of direct current, and empirical rules for quantifying lesion size based on current and time were developed.[1,2] One of the first uses in humans was for the management of trigeminal neuralgia in 1931 when a direct current was delivered through a needle with a 10 mm uninsulated tip placed in the Gasserian ganglion.[3] This technique produced lesions of unpredictable size.[4] The use of high frequency electric current was later found to produce lesions with a more predictable size.[5] Because frequencies of 300–500 kHz were also used in radio transmitters, the current was called radiofrequency (RF) current. Later, temperature monitoring was suggested to be the most important parameter to obtain a standardized lesion size.[6]

In pain management, RF was first used for percutaneous lateral cordotomy to relieve unilateral pain in cancer patients.[5] A few years later, RF treatment of trigeminal neuralgia was described.[7] The first use of RF current for spinal pain was reported by Shealy,[8] who performed RF lesioning of the medial branch for lumbar zygapophyseal joint pain. Another application for spinal pain was introduced by Uematsu,[9] who described RF lesioning of the dorsal root ganglion (DRG).

At the end of the 1970s, percutaneous cordotomy and RF treatment of the Gasserian ganglion were the only widely accepted RF procedures. A turning point came in 1980, when small-diameter electrodes, known as the Sluijter Mehta Kit (SMK) system, were introduced for the treatment of spinal pain.[10] The system consists of a 22-gauge disposable cannula with a fine thermocouple probe inside for measurement of temperature. The smaller electrode size resulted in diminished discomfort during the procedure. Because there was less risk for mechanical injury to major nerve trunks, targets in the anterior spinal compartment were no longer off-limits, and procedures such as RF lesions adjacent to the DRG (RF-DRG) and lesions of the communicating ramus,[11,12] and sympathetic chain became part of the treatment armamentarium.

Over the years, the concept that the clinical effect of RF current was caused by the formation of heat had not been challenged. A selective effect of heat on thin nerve fibers was thought to interfere with the conduction of nociceptive stimuli.[13]

The role of heat was finally questioned for several reasons. First, the classic concept presupposes a strict configuration: the RF lesion must be made in between the nociceptive focus and the central nervous system (CNS). However, RF lesions were also successful when performed distal to the nociceptive focus and the CNS. For example, in the treatment of acute radicular pain from a herniated disk, the electrode is placed distal to the nociceptive focus.[14] Second, RF-DRG induces only transient sensory loss, which is possibly heat related, whereas the pain relief may be of much longer duration.[15] Finally, no differences in outcome were noted when two different tip temperatures (i.e. 40°C and 67°C) were applied.[16] It is against this background that pulsed radiofrequency (PRF) treatment was developed.[17] PRF delivers strong, fluctuating electric fields while the temperature effects are kept to a minimum. PRF was conceived as a novel, potentially safer mode of administration of RF energy.[18–20] It can be specifically useful for treatments in which RF lesioning is not indicated, such as peripheral neuropathies, atherogenic pain, painful trigger points, and application to the DRG in patients with neuropathy or radicular pain.

Radiofrequency Generator System

A modern RF generator has the following components:

- Continuous online measurement of impedance
- Nerve stimulation
- RF delivery mode
- Pulsed current delivery mode
- Monitoring of voltage, current, and wattage during the RF procedure
- Temperature monitoring

Electrical impedance is measured to confirm the continuity of the electrical circuit. After placement of the needle under fluoroscopic control, nerve stimulation is performed to confirm the proper position of the electrode. Stimulation is carried out at 50 Hz to ensure proximity of the electrode to sensory fibers; 2 Hz stimulation is performed to detect muscle contractions, which indicates that the position of the needle is too close to motor fibers. If an electrode is actually resting on a nerve, the minimum stimulation level required to produce a discharge is 0.25 V.[21] At a distance of 1 cm from the nerve, 2 V would be required. Thus the stimulation threshold is an indicator of the distance of the electrode from the nerve. Temperature is measured with a thermocouple electrode. A thermocouple electrode consists of a junction of two dissimilar metal elements and produces a voltage proportional to temperature.

Theoretical Aspects of Radiofrequency Treatment

Continuous Radiofrequency Treatment

The generator establishes a voltage gradient between the (active) electrode and the (dispersive) ground plate. RF current flowing through the tissue results in an alternating electric field. This electric field creates an electric force on ions (electrolytes) in the tissue

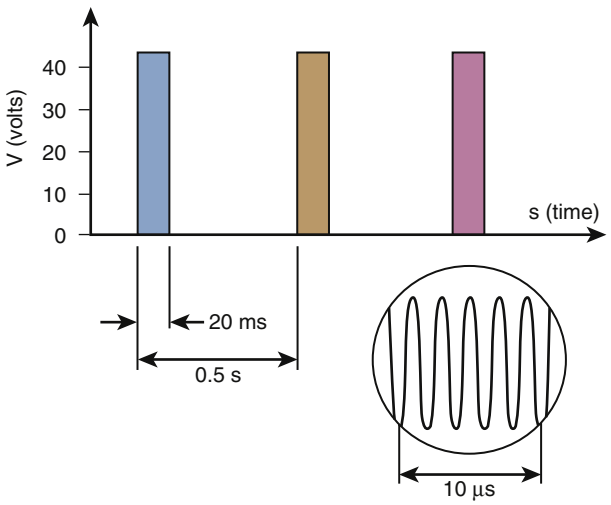
that causes the ions to move back and forth at a high rate. Frictional dissipation of the ionic movement within the fluid medium results in tissue heating. The lesion size depends on the temperature of the tip of the electrode, and tip temperature depends on the amount of power delivered. Other factors influence lesion size, for instance, heat and the type of tissue. Heat is removed from the lesion area by conductive heat loss and blood circulation (heat "washout"). The larger the heat washout, the smaller the lesion will be for a given tip temperature. The type of tissue factors influences heat washout. For example, bone is an effective heat insulator, and therefore RF lesions close to the bone will have less washout. Similarly, segmental blood vessels, which lie in close relationship to the DRG, may cause more heat washout and thereby reduce the size of the lesion.[22]

Pulsed Radiofrequency Treatment

The treatment effect of PRF is based on the dual effect of exposure of the tissue to RF fields (Fig. 66.1). Besides the ionic friction that causes the production of heat, there is an independent electric field effect. The mechanism of this electric current effect is thought to be an alteration in synaptic transmission in a neuromodulatory type of effect.[18,19,23] Alterations have been found in peripheral sensory neurons,[24] the DRG,[25,26] neurotransmitters and microglia in the dorsal horn,[27] descending inhibitory pain pathways, and the CSF.[28,29]

Practical Considerations

Although no clinical complications have been reported, this technique is considered minimal neurodestructive.[30] Therefore it may be wise to avoid ultralow sensory thresholds (<0.05 V) because such values may reflect intraneural electrode placement.[22] In a small proportion of procedures, the mean tip temperature exceeds 42°C at some point during the PRF procedure. In this case, power output should be decreased as a precaution. This can be done by lowering the voltage or by decreasing either the duration of the active cycle (typically 20–30 ms) or the frequency of the cycle (typically 2 Hz).



• **Figure 66.1** Schematic drawing of the duty cycle during pulsed radiofrequency treatment. There are two active cycles per second of 20 ms each. During the active phase, radiofrequency current is delivered at the normal frequency of 500,000 Hz. (Based on Sluijter ME. *Radiofrequency: Part I.* Meggen, Switzerland: Flivopress; 2001, with permission of the publisher.)

It is not desirable to adjust the voltage during a PRF procedure to reach the mean tip temperature since the mean tip temperature does not affect the outcome of the procedure.[31] Because there is a large variation in heat washout, large and unpredictable variations in voltage will occur. There is no optimal duration of treatment. However, durations of 240 s are often reported. Typical PRF treatment settings are 45 V for 240 s at 2 Hz and 20 ms pulse width.

Cooled RF

The use of cooled radiofrequency treatment was first described for the treatment of low back/sacroiliac joint pain. Later, it was introduced for the treatment of chronic knee pain.[32–34]

Cooled electrodes increase lesion size by removing heat from adjacent tissue and allowing power delivery to be increased without tissue scarring and high impedance.[35] A randomized controlled trial (RCT) study showed a higher success percentage and possibly a longer effect with the use of cooled radiofrequency for the treatment of knee pain.[36] There is an increasing interest in the use of cooled RF.

Indications for Radiofrequency Treatment

Radiofrequency Treatment Procedures On The Head

Radiofrequency Treatment of the Gasserian Ganglion

Trigeminal Neuralgia

Patients with trigeminal neuralgia have brief episodes of sharp, shooting pain in one or more of the trigeminal divisions that are typically provoked by touch. This so-called trigger area need not be in the division where the patient experiences pain. In the classic case, the patient is free of pain between episodes. However, residual pain has been reported in 42% of cases.[37] These patients have been described as having a combination of trigeminal neuralgia and atypical facial pain. Trigeminal neuralgia predominantly occurs in older age groups (50+ years), although it may occasionally be seen in very young patients. It is thought to be caused by vascular compression of the trigeminal root. In patients with multiple sclerosis, it occurs frequently and may indeed be the first symptom of the disease. In a study evaluating the clinical characteristics of patients with trigeminal neuralgia, 22 had multiple sclerosis. Six of them had atypical trigeminal neuralgia, and 16 had signs of brainstem involvement.[38] It is not clear whether the pain is caused by plaques in the CNS in these patients, but clinically there was no distinction between patients with and without brainstem involvement. Trigeminal neuralgia may also be caused by a primary brain tumor (acoustic neuroma), which should always be excluded before symptomatic treatment is considered (red flag).

Treatment. In younger patients, posterior fossa craniotomy with microvascular decompression (MVD) is the treatment of choice.[39] This treatment has a high rate of success and avoids the sensory loss that is one of the consequences of thermocoagulation of the ganglion. This procedure has a low complication rate. Complications are mostly serious neurologic deficits.[40] In patients with multiple sclerosis, the procedure should be combined with partial sectioning of the trigeminal nerve.[41] This could be an indication of a more central mechanism in these patients. Pain relief is substantially longer after microvascular decompression than after thermocoagulation of the ganglion. If the pain recurs, recurrent vascular compression is seldom found during reoperation.[42] In such cases, partial sectioning of the nerve could be performed. However, other forms of treatment such as thermocoagulation are generally recommended because the incidence of

complications of MVD is distinctly higher after reoperation.[42,43] The outcome of thermocoagulation in operated patients is less favorable.[44] PRF seems a safer alternative that was shown to be effective in case reports.[45,46] An RCT comparing RF with PRF found a much shorter duration of efficacy for PRF.[47] More recently, an RCT that compared short RF, long RF, and PRF showed that all groups experienced significant differences in pain than baseline. No differences were found between the groups.[48] A retrospective study and an additional RCT found that high voltage PRF resulted in a longer-lasting pain relieving effect than standard voltage PRF.[49,50] The choice between MVD, RF, and PRF treatment of the Gasserian ganglion is a clinical decision in which age, physical condition, and personal preference of the patient have to be taken into account.

Evidence. Following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system on assessing the quality of evidence, there is a low quality of evidence that RF of the Gasserian ganglion reduces the pain of patients suffering from idiopathic trigeminal neuralgia for at least six months. There is evidence of very low quality that PRF is effective in the treatment of trigeminal neuralgia.[51] However, there is extensive experience with RF treatment of trigeminal neuralgia. A review of 25 years' experience in 1600 patients undergoing percutaneous RF trigeminal rhizotomy for idiopathic neuralgia indicated acute pain relief in 97.6% and continued complete pain relief at five years' follow up in 57.7%.[52] Comparisons with other techniques are based mainly on retrospective evaluations.[53–59]

Comprehensive considerations for the usage of continuous radiofrequency (CRF) or pulsed radiofrequency (PRF) treatment in idiopathic trigeminal neuralgia are outlined by Guo et al.[60]

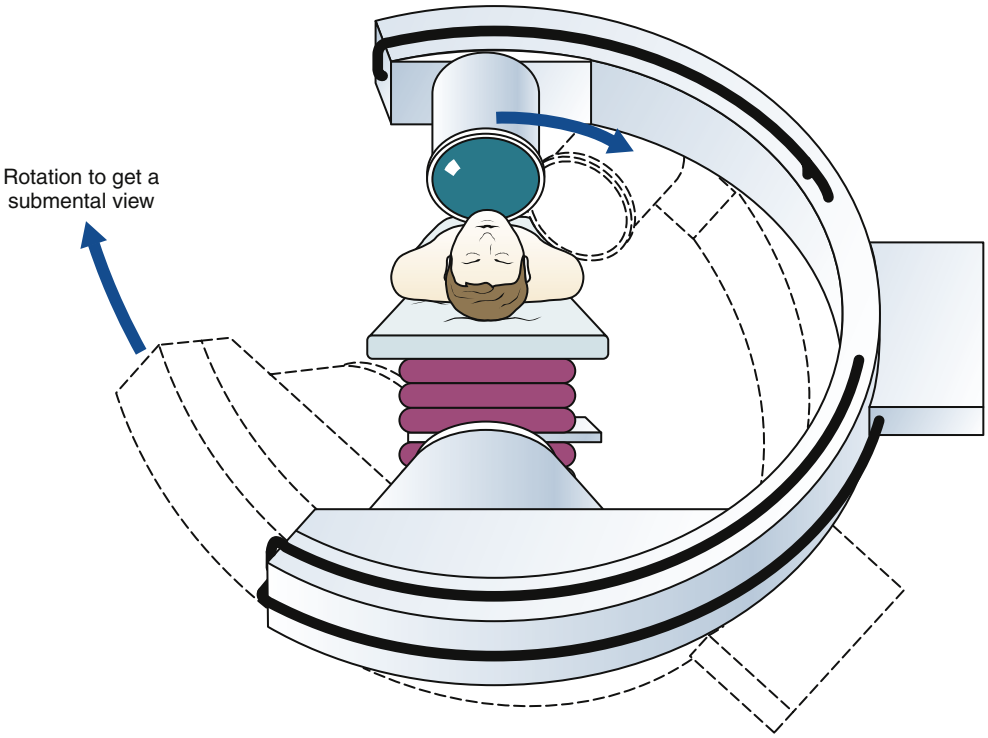
Procedure. The technique for placing a radiofrequency needle in the Gasserian ganglion is as follows:

The oval foramen is visualized first by using a tunnel view technique. To attain this, the direction of the x-rays should be reversed from the normal configuration because the image intensifier is too bulky to avoid contact with the patient's chest (Fig. 66.2). The position of the C-arm should be adjusted until the oval foramen is identified just medial to the mandibular processes and just lateral to the maxilla.

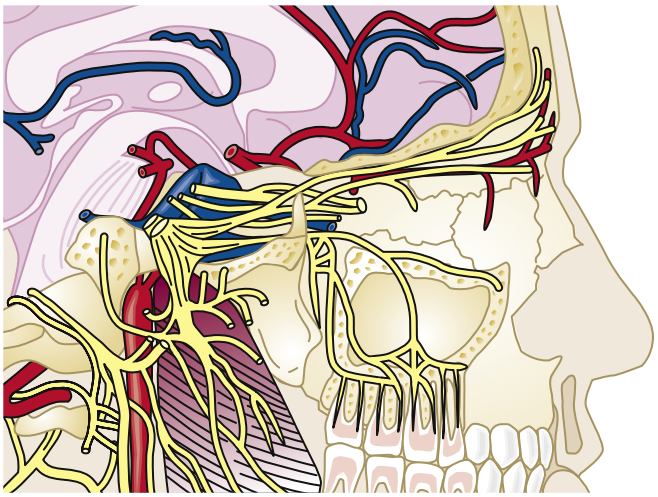
The shape of the foramen varies with the angle of the x-rays in the horizontal plane. A more vertical direction will transform the foramen into a round, almost circular shape. A more horizontal direction will make the foramen flat, like a split. The C-arm should be adjusted so that the foramen optimally has an oval shape. The skin entry point is now marked over the target point and is located lateral to the corner of the mouth. The entry point may be just superior to the mandible, but it also may be much more superior, close to the maxilla (Fig. 66.3).

Adverse Events and Complications. RF treatment of the Gasserian ganglion is associated with very low morbidity and virtually no reported mortality.[61] Reports vary considerably regarding recurrence of pain. This may be because of variations in technique. If a dense sensory loss is produced, there is a low incidence of recurrence.[7,62] However, loss of facial sensation and the accompanying paresthesia account for 80% of the side effects of the procedure with an incidence of 18.8%.[61] If RF treatment with a less intense lesion is performed, it might be associated with a lower incidence of paresthesia but potentially earlier recurrence. Other complications include corneal hypesthesia (6.6%), masseter weakness and paralysis (4.1%–6.2%), anesthesia dolorosa (0.6%–1%), keratitis (0.6%–1.2%), transient paralysis of cranial nerves III and IV (0.8%), CSF leak (0.11%), hearing loss (0.13%), and meningitis (0.02%).[52] A much less frequent complication is permanent palsy of the abducens nerve.[63]

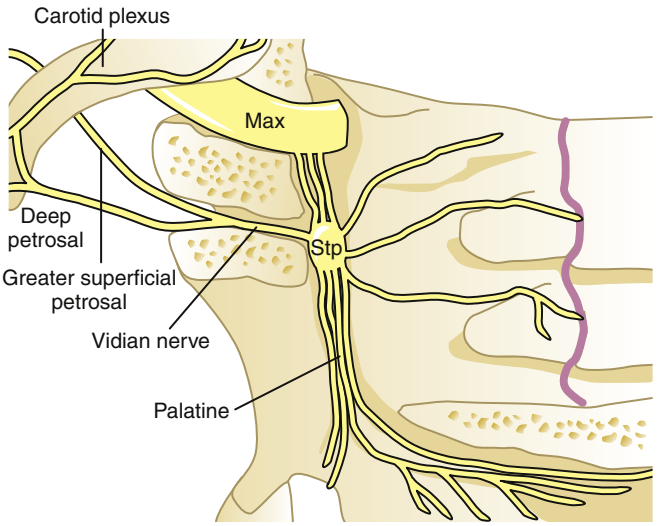
No complications have been reported with PRF treatment of the Gasserian ganglion.[45–50]



• **Figure 66.2** Schematic drawing of the fluoroscopy position for performing a radiofrequency procedure on the Gasserian ganglion.



• **Figure 66.3** Anatomy of the gasserian ganglion and various trigeminal divisions. (From Sluijter ME. *Radiofrequency: Part I*. Meggen, Switzerland: Flivopress, 2001; with permission of the publisher.)



• **Figure 66.4** Connections of the sphenopalatine ganglion. (From Sluijter ME. *Radiofrequency: Part I*. Meggen, Switzerland: Flivopress; 2001, with permission of the publisher.)

Radiofrequency Treatment of the Pterygopalatine (Sphenopalatine) Ganglion

The pterygopalatine ganglion is a parasympathetic ganglion located in the pterygopalatine fossa just beneath the maxillary nerve. It is in or close to the foramen that connects the pterygopalatine fossa to the nasal cavity. Preganglionic fibers reach the ganglion from the facial nerve through the greater superficial petrosal nerve and the nerve of the pterygoid canal. There are also connections through the deep petrosal nerve that joins with the greater superficial petrosal nerve to form the Vidian nerve (Fig. 66.4). Many afferent fibers originating from the nasal mucosa, the soft palate, and the pharynx cross the ganglion on their way to the maxillary nerve and eventually to the Gasserian ganglion.

Cluster Headache

Treatment and Evidence. The rationale for RF treatment of cluster headaches is based on parasympathetic symptoms during an attack.[64] Following the GRADE system, there is a very low quality of evidence that RF of the pterygopalatine ganglion reduces intensity and frequency of cluster headache attacks up to 18 months.[51,64–66] A retrospective study of 56 patients with episodic and 10 patients with chronic cluster headache treated by RF treatment of the pterygopalatine ganglion and followed 12–70 months. In the group with episodic cluster headache, 60.7% experienced complete pain relief, while only three out of ten patients with chronic cluster headache had the same result.[64] Another retrospective study of 15 patients reported significant improvement in both mean attack intensity and mean attack frequency for up to 18 months.[65]

Since cluster headache is a very rare but severe clinical condition, the authors recommend that RF of the pterygopalatine ganglion could be used in patients with cluster headache refractory to conservative treatment.

Persistent Idiopathic Facial Pain

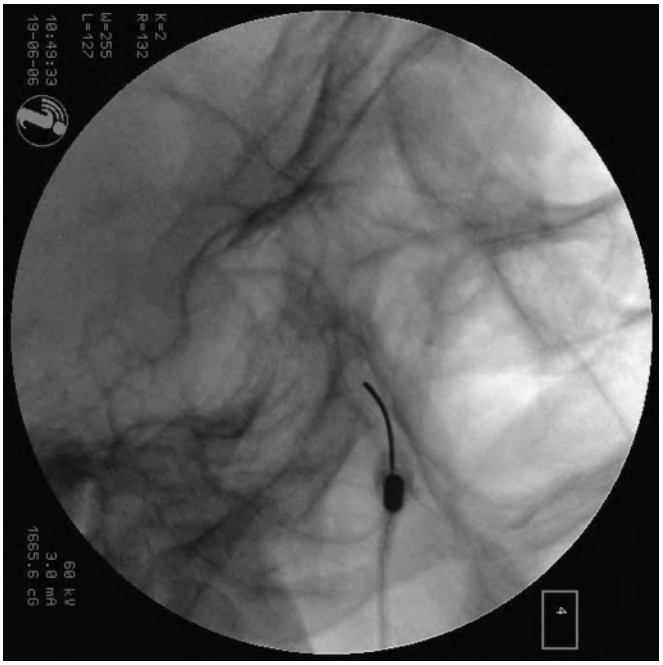
In a retrospective study assessing the effect of RF treatment of the pterygopalatine ganglion on persistent idiopathic facial pain (PIFP), 60% (nine out of 15 patients) showed considerable pain relief. However, repeated RF treatment procedures were needed in most cases.[67] Treatment of atypical facial pain in the second division of the trigeminal nerve using RF of the pterygopalatine ganglion has also been described.[66] A case report on PRF treatment of the pterygopalatine ganglion for posttraumatic headache described 17 months of pain relief.[68] Analysis of PRF treatment of the pterygopalatine ganglion in 30 patients suffering from chronic head and facial pain showed complete relief of pain in 21% and mild to moderate relief in 65%.[69] In a case series ($N = 8$) on refractory chronic short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and with cranial autonomic symptoms (SUNA) reported an average improvement in pain of 57% (30%–100%), with an average duration of six (2–10) months.[70]

Evidence for the use of PRF is weak, but given the safe character of this treatment, the authors recommend the use of PRF for these aforementioned conditions.

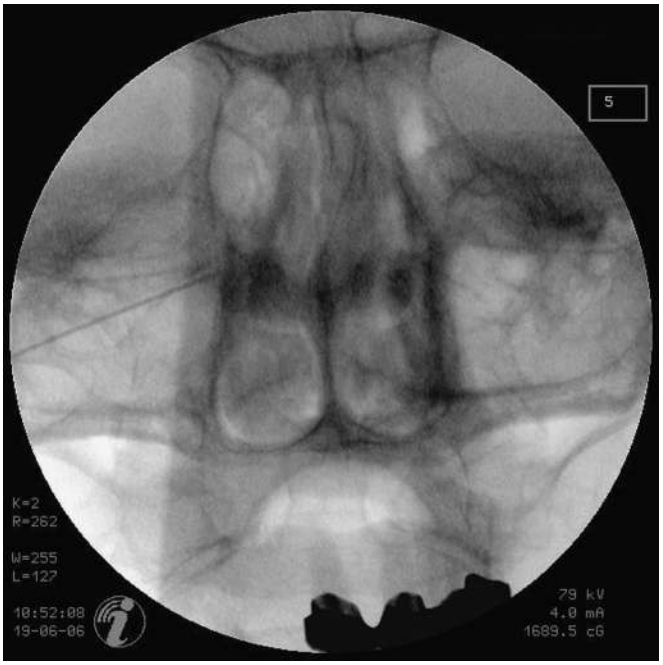
Procedure. The patient is placed in a supine position with the head immobilized. The pterygopalatine fossa is identified on the lateral fluoroscopic image, and a line overlying the fossa is drawn on the skin. The intersection of this line with the inferior edge of the zygomatic arch is the entry point. After anesthetizing the skin, a 10 cm RF cannula with a 5 mm active tip is inserted at this point and then carefully advanced under lateral fluoroscopic control in a superior and anterior direction to enter the pterygopalatine fossa (Fig. 66.5). As soon as the fossa is entered, the cannula contacts the maxillary nerve, and the patient reports paresthesia, 1–2 mL of 2% lidocaine is injected. The cannula is advanced further until the tip reaches the pterygopalatine fossa, which is located in the anterior superior corner of the fossa. The tip needs to pass the rim of the fossa to prevent damage to the maxillary nerve during the lesion.

The C-arm of the image intensifier is then placed in the anteroposterior (AP) position. The tip of the cannula should now be projected over the lateral wall of the nasopharynx (Fig. 66.6).

The stylet is removed and replaced with a thermocouple RF probe. The position of the electrode is verified by electrical stimulation at 50 Hz, and this usually results in paresthesia inside the nose at 0.2–1.0 V. Paresthesia occurring at the outside of the cheek or upper lip indicates stimulation of the maxillary nerve



• **Figure 66.5** Needle placement in the pterygopalatine fossa.



• **Figure 66.6** Anteroposterior view of needle placement in the pterygopalatine fossa.

and thus that the tip of the needle is too far lateral. If the patient reports paresthesia in the palate, the cannula is advanced a few millimeters. Treatment consists of three consecutive lesions performed at 70°C–80°C for 60 s.[64] In between these lesions the cannula is slowly advanced (1–3 mm).

Adverse Events and Complications. Total destruction of the pterygopalatine ganglion causes dryness of the eye, an "open nose" since the mucosa has less inclination to swell, and numbness of the soft palate. However, dryness of the eye is unusual after a thermal RF lesion. Numbness of the soft palate is usually temporary, with gradual recovery occurring over four to six weeks. Sometimes loss of taste can be permanent. No complications have been reported after PRF treatment of the pterygopalatine ganglion.

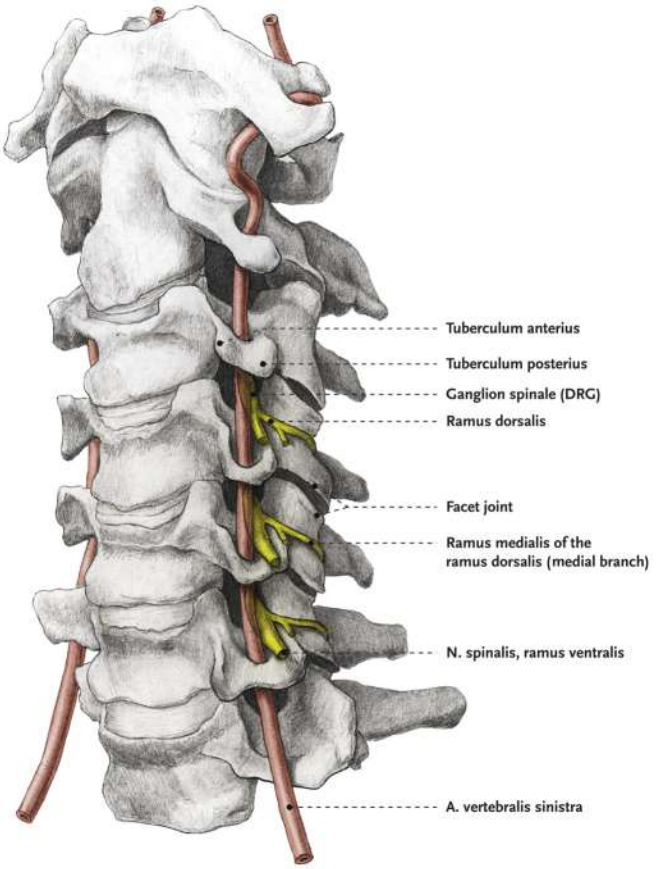
Radiofrequency Treatment Procedures on the Cervical Spine

Cervical Facet (Zygapophyseal) Joint Pain

Facet pain is discussed in more detail in Chapter 31.

The most common symptom of pain arising from the cervical facet joints is unilateral pain that does not radiate beyond the shoulder. Pain emanating from the cervical facet joints can be referred to as the occiput, the interscapular region, or the shoulder girdle regions, depending on which cervical facet joint is involved.[71–74] Pain from the higher cervical facet joints may be the origin of cervicogenic headache.[75] Physical examination of the cervical spine usually shows paravertebral tenderness and limitation of rotation and retroflexion.[76] Computed tomography and magnetic resonance imaging may reveal morphologic abnormalities of the facet joints. However, degenerative changes of the cervical spine are present in asymptomatic patients, thus supporting the lack of correlation between radiologic findings and pain.[77,78]

Indications for RF treatment of the medial branches that innervate the cervical facet joints are degenerative and posttraumatic neck pain (i.e. whiplash-associated disorders).[79–82] The anatomy of the cervical spine is illustrated (Fig. 66.7).[82,83] RF treatment of the cervical medial branches is aimed at reducing nociceptive signals



• **Figure 66.7** Anatomy of the cervical spine. *DRG*, Dorsal root ganglion. (Illustration courtesy of Rogier Trompert Medical Art. Available at: www.medical-art.eu.)

from the spinal facet joints and is usually performed at two or three segmental levels.

Evidence

Percutaneous RF treatment of cervical facet-mediated pain has been studied intensively. The data from original articles were summarized in systematic reviews.[84–87,88]

Following the GRADE systematics, there is a low quality of evidence that RF treatment of the medial branch reduces cervical facet joint pain.[51] Only one RCT has evaluated RF treatment of the ramus medialis (medial branch) of the ramus dorsalis in patients with whiplash-associated disorders.[79]

The effectiveness of RF treatment for degenerative neck pathology was shown in observational studies.[76,89,90] A retrospective chart analysis of the effect of repeated RF facet treatments illustrated that the mean duration of effect of the first intervention was 12.5 months. The procedure can be repeated when pain recurs, with similar success. Patients who respond positively to the first intervention received up to six additional interventions. After each RF intervention, more than 90% of the patients had satisfactory pain relief, and the duration of effect was between eight and 12 months.[91]

Van Suijlekom and coworkers evaluated the effect of RF lesioning of the medial branch of the dorsal ramus at the C3–6 levels for the treatment of cervicogenic headache.[92] In this study the posterolateral approach was used. They demonstrated that RF cervical facet treatment leads to a significant reduction in headache severity, number of days with headache, and analgesic intake in patients with cervicogenic headache diagnosed according to the criteria of Sjaastad and colleagues.[75] In a randomized, double-blind, sham-controlled study on RF treatment of facet joints C2–3 for the treatment of cervicogenic headache, 12 patients were included and monitored for 24 months. A slight improvement was noted in the RF group at three months, whereas no differences were seen during the remaining follow up period.[93] In contrast, Haspeslagh and associates[94] could not find evidence that RF treatment of the cervical facet joints, followed by cervical DRG when necessary, is better than steroid injection at the greater occipital nerve.

Two other observational studies with 104 patients,[95] and 130 patients[96] showed significant pain relief. In the first study, 74% and 61% of the patients attending two different practices had complete pain relief or at least 80% pain relief for at least six months. In this study, the duration of the effect was 17–20 months for the first RF treatment and 15 months for the repeat treatment.[95] The second study showed success (average pain relief of 88%) in 76% of the patients that lasted for 12 months.

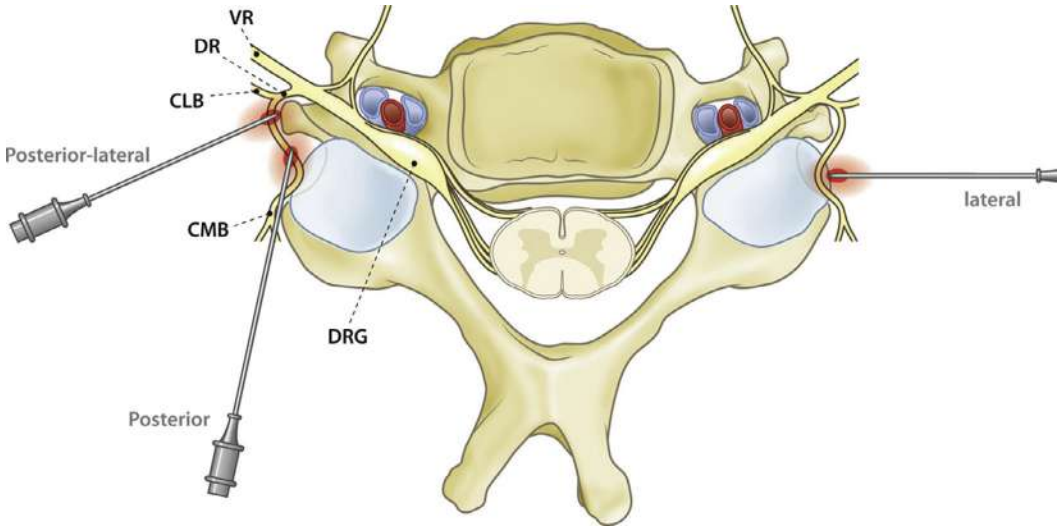
An additional exploratory study evaluated the therapeutic effect and its duration of RF treatment, using the single posterior-lateral approach in patients suffering from facet joint degeneration. Overall pain relief was reported in 55.4% at two-month follow up. At three-year follow up, 30% of the patients still reported pain reduction.[97]

Procedure

Several approaches can reach the medial branch of the dorsal ramus at the upper and middle cervical area.[98]

The technique that is most used in many observational studies is the posterior technique.[88,99]

The posterolateral technique**,** using oblique fluoroscopy, was first published in 1980 by Sluijter.[100] The patient is positioned in a supine position. The neuroforamen is visualized with an oblique X-ray projection. The target point for RF denervation of the cervical medial branch (CMB) is the base of the superior articular process, in oblique view posterior to the caudal part of the neuroforamen. The needle insertion point is estimated somewhat posterior and caudal to the target point. After insertion, the RF probe is advanced at an anterior angle to the frontal plane until bony contact is achieved. The angulation is necessary to get a more perpendicular position of the needle endpoint to the CMB. The target point is at the anterolateral side of the facet column close to the neuroforamen and the expected course of the CMB (Fig. 66.8). Then, with the X-ray projection in anteroposterior (AP) view, the RF probe is positioned in the concavity of the articular pillars of the cervical spine, taking care not to enter the neuroforamen. A safe distance between the needle tip and the cervical segmental nerve can be achieved in this way. Additionally, 50 Hz and 2 Hz stimulation are performed by a lesion generator to avoid a position



• **Figure 66.8** The three currently used techniques for radiofrequency denervation of the CMB: the posterolateral, the posterior, and the lateral approach. *VR*, Ventral ramus of the cervical segmental spinal nerve; *DR*, dorsal ramus of the cervical segmental spinal nerve; *CLB*, cervical lateral branch from the dorsal ramus; *CMB*, cervical medial branch from the dorsal ramus; *DRG*, dorsal root ganglion.

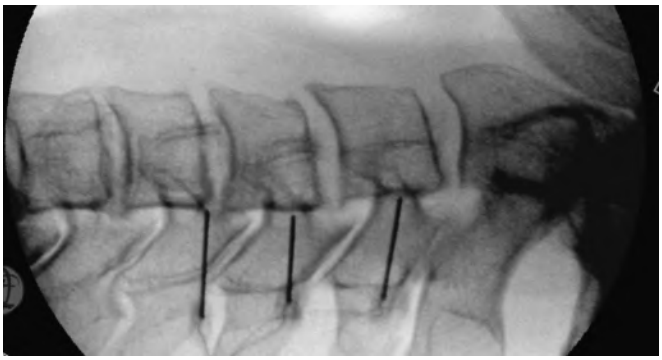
too close to the cervical segmental nerve. Then a single RF lesion is made at the described target point.

The posterior technique was first published in 1996 by Lord et al.[79] This technique is adopted by the Spine Intervention Society (SIS) and is part of SIS technique guidelines.[99] The patient is positioned in a prone position. The posterior technique is described as a two-stage procedure: first, in a lateral X-ray projection, a needle is positioned at the anterior side of the facet column, roughly at the same location as in the posterolateral technique. Then with the X-ray projection in anteroposterior (AP) view, an RF probe is advanced in a sagittal pass parallel to the expected course of the CMB (Fig. 66.8). Extensive and multiple lesions are made along the expected course of the CMB because there is a substantial inter-individual anatomical variation in the course of the CMB over the waist of the facet column.[101,102]

The lateral technique is first described as a technique for diagnostic blocks of the CMBs.[103,104] Later on, this technique was also described as a technique for RF treatment.[105–109] The patient can be positioned in a supine or lateral position. The X-ray beam is in a lateral position; thus this is a "coaxial" also called "tunnel view" technique. The target point of the needle is the midpoint of the rhomboid-shaped silhouette of the facet column (Fig. 66.8).

We developed a new approach of the posterolateral technique with a lateral projection. The target point is the same as in the technique as described by Sluijter. For this technique, the patient is also positioned supine on the operating table.[98]

The domelike structure between C1 and C2 should be aligned without any double contours to treat the upper cervical levels. Usually, the facet joint space of C3–4 is clearly visible, also without double contours. Adjustments of the C-arm are often necessary for the C4, C5, and C6 levels to align the facet joint spaces and the facetal column. In this position, the anterior and posterior tubercles of the neuroforamen can be seen projected over the vertebral body. The medial branch runs just above the posterior tubercle, midway between the facet joints. Needle entry points should be at the dorsal side of the facetal column in a virtual vertical line exactly between the facet joint spaces. Under fluoroscopic guidance, the needle electrode is carefully placed in a slightly anterior horizontal direction until contact is made with the facetal column (Fig. 66.9). The tip of the needle should be at or just above the posterior tubercle, midway or slightly rostral between the facet joint spaces. To confirm that the tip of the needle is close to the segmental nerve but not in the neuroforamen, the C-arm is placed in an approximately 30-degree oblique position in such a way that the projection of the contralateral pedicles is more or less anterior to the vertebral body (Fig. 66.10). This position is sometimes

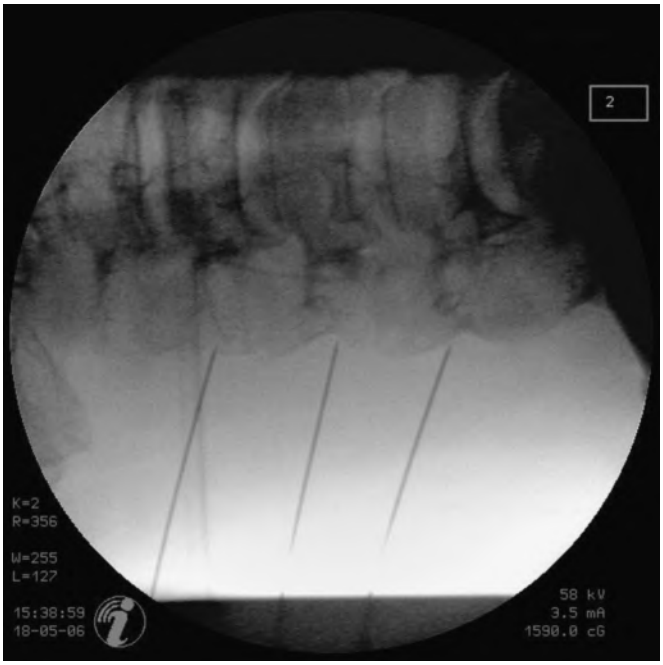


• **Figure 66.9** Fluoroscopic image of the position of the needle for a cervical medial branch procedure via a lateral approach.

• **Figure 66.10** Fluoroscopic image of the position of the needle for a cervical medial branch procedure.

preferred for treatment of the C6 and C7 levels because of over projection of the shoulders on the lateral view.

Positioning the C-arm in the AP direction should confirm the position of the tip of the needle adjacent to the concavity ("waist") of the articular pillars of the cervical spine at the corresponding level (Fig. 66.11). Electrical stimulation is performed to confirm the correct needle position when optimal anatomic localization of the needles is achieved. An electrical stimulation rate of 50 Hz should elicit a response (tingling sensation) in the neck at less than 0.5 V. Stimulation at 2 Hz is performed to confirm



• **Figure 66.11** Anteroposterior view of the cervical spine–needle position for a procedure on the medial branch.

accurate needle position. Contractions of the paraspinal muscles will be noticed. Muscle contractions in the arm indicate placement of the needle too close to the exiting nerve. In this case, the needle should be repositioned more posteriorly. Once proper positioning of the needle is confirmed, the medial branch of the dorsal ramus is anesthetized with 1–2 mL of local anesthetic solution (1% or 2% lidocaine). An 80°C RF thermal lesion is made for 60–90 s at each level.

Adverse Events and Complications

Complications are rare.[88] Nevertheless, one should be aware that the vertebral artery may be punctured if the needle is pushed too far anterior into the intervertebral foramen. The position of the tip of the needle should be verified with AP fluoroscopy to prevent intrathecal injection of the local anesthetic. In an observational study, the incidence of inadvertent intravascular penetration for medial branch blocks at a cervical level was reported to be 3.9%, comparable to the incidence at a lumbar level (3.7%).[110] Some patients experienced short-term vasovagal reactions. Intravascular uptake of local anesthetic and contrast solution was thought to be responsible for the false-negative diagnostic blocks. No systemic effects were reported.[110] Monitoring of the saturation level and availability of resuscitation equipment are essential.

Infections have been described, but the incidence is unknown and probably very low.[111,112] Other complications of facet joint interventions are related to needle placement and drug administration. They include dural puncture, spinal cord trauma,[113] spinal anesthesia, chemical meningitis, neural trauma, pneumothorax, facet capsule rupture, and hematoma formation.[87] After RF treatment, burning pain is regularly reported postoperatively. However, this pain disappears in one to three weeks.[94,114] There are no high quality incidence data on side effects and complications following cervical RF treatment of the ramus medialis (medial branch) of the ramus dorsalis.[88] At the lumbar level, the incidence of complications was lower than 1%.[82]

Radiofrequency Treatment of the Cervical DRG

Cervical Radicular Pain

Cervical radicular pain is a common pain syndrome, but it must be distinguished from cervical radiculopathy. Cervical radiculopathy implies an objective loss of sensory and/or motor function. In practice, both disorders may occur simultaneously. Radicular pain is a symptom that is caused by ectopic impulse formation. This may result from the same clinical entities such as narrowing the intervertebral foramen, intervertebral disc herniation, and radiculitis because of arthritis, infection, or inflammatory exudate. There is little published information on the natural history of cervical radicular pain. Bland estimated that 9% of all men and 12% of all women experience this pain at some time in their lives.[115] Later, in 1994, Radhakrishnan and associates published a population-based survey.[116] This epidemiologic survey found the annual incidence of cervical radiculopathy to be 83.2 per 100,000 population between 13 and 91 years of age. The most frequently involved levels are C7 in 45%–60% of the cases, level C6 is involved in 20%–25% of the cases, and levels C5 and C8 each represented approximately 10% of the cases.[31]

Cervical radicular pain is perceived in the upper limb as shooting or electric in quality. The distribution of the pain radiation pattern is indicative of the involved level.[117] This can be summarized as pain from C4 is restricted to the neck and suprascapular regions. Pain from C5 extends in the upper arm, and pain from C6 and C7 extends from the neck and shoulder into the forearm and hand.[118] Confirmation of the involved level can be obtained by diagnostic nerve blocks.[111,119–121]

Diagnosis of cervical radicular pain and radiculopathy requires complete history taking and clinical diagnosis using standardized methods of physical examination,[121,122] medical imaging, and electrophysiologic investigation.

The pathophysiologic mechanisms of cervical radicular pain are two-fold: (1) nucleus pulposus material leaking onto the nerve root and/or (2) compression of the nerve root by anatomic abnormalities. These pathogenic mechanisms induce two processes in the nerve: (1) an inflammatory reaction and (2) changes in ion-channel functioning.[122] In patients with persisting cervical radicular pain of a duration longer than three months despite conservative treatment, interventional pain management with radiofrequency can be considered.

Evidence for Radiofrequency Treatment Adjacent to the Cervical DRG

Following the GRADE system, there is moderate quality of evidence that RF of the cervical DRG reduces radicular pain.[51] Two RCTs report on the use of radiofrequency adjacent to the cervical DRG.[16,119] The first study[119] found radiofrequency treatment adjacent to the cervical spinal ganglion (DRG) to be superior to sham eight weeks after the intervention.

The second study compared RF with an electrode tip temperature of 40°C with RF at 67°C.[16] At six weeks and three months after treatment, there was a significant decrease in the visual analog scale pain score in both groups. There was no significant difference in outcome between the two groups.

Continuous thermal radiofrequency treatment uses neurodestructive electrode tip temperature, which results in nerve damage and potentially can cause deafferentation pain. This is the reason why continuous RF is less frequently used since the development of the less neurodestructive pulsed radiofrequency treatment.

Evidence for Pulsed Radiofrequency Treatment Adjacent to the Cervical DRG

Following the GRADE systems, there is moderate quality of evidence that PRF of the cervical DRG reduces radicular pain. A recent systematic review[123] found one RCT,[124] three before and after comparisons,[125–127] one case series,[128] on the use of PRF adjacent to the DRG for the treatment of cervical radicular pain. In a clinical audit 18 patients, with cervicogenic headache or cervicobrachialgia who failed conservative treatment underwent PRF treatment adjacent to the cervical DRG.[129] Seventy-two percent of the patients had a minimum reduction in pain of at least 50% at eight weeks. At one year, 33% of the patients rated the treatment outcome as good or very good. The RCT included 23 patients who were randomly assigned to PRF or sham intervention. The level to be treated was confirmed by means of diagnostic blocks.[124] At the three-month follow up, patients in the PRF group had significantly more pain reduction and a significantly better global perceived effect. The SF-36 domain vitality was significantly better in the PRF group. The need for pain medication was reduced in the PRF group at six-month follow up.[124] The systematic review concluded that there were positive efficacy findings in all the analyzed studies.[123]

A case series of 43 patients[125,127] suggested that more than 60% of patients benefited in terms of more than 50% pain relief or treatment success after six months with no serious adverse effects reported. This relief appears to be sustained at one year follow up

(12 of 21 patients). A meta-analysis of studies reporting the effect of PRF-DRG in patients with cervical radicular pain because of disc herniation, or cervical spinal stenosis included four studies: one RCT, two observational studies, and one retrospective study, showed a significant pain reduction at two weeks, one, three, and six-month follow up.[130] A recent retrospective study on 59 patients treated with PRF-CDRG for cervical radicular pain showed that 67% of the patients experienced >50% pain reduction. This effect lasted for 37 weeks.[131] In these studies, no motor or sensory complications were observed.

In summary, there is moderate evidence that PRF treatment of the DRG (PRF-DRG) on a cervical level is as effective as RF-DRG. However, PRF-DRG is safer and has fewer side effects. Therefore the authors suggest that cervical radicular pain be treated with PRF-DRG and not with RF-DRG.

Procedure

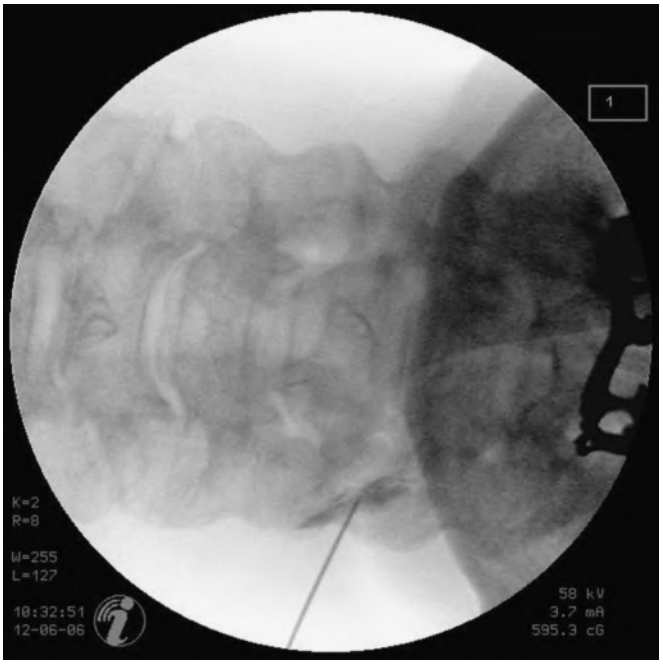
To perform a *diagnostic segmental nerve block,* a viewing technique is used in which the C-arm is positioned so that the x-rays are parallel to the axis of the intervertebral foramen. This axis points 25–35 degrees anteriorly and 10 degrees caudally. With the C-arm in this position, entry is determined by projecting a metal ruler over the caudal and posterior part of the foramen. A 50 mm, 22-gauge neurography needle is carefully introduced parallel to the beam of the x-rays. The direction of the x-rays is then changed to the AP position, and the cannula is introduced further until the tip is projecting just lateral to the facetal column. After the segmental nerve has been identified with 0.4 mL of iohexol contrast medium, 0.5 mL of 2% lidocaine is slowly infiltrated around the nerve. The resultant radiopaque mixture is closely observed during injection to avoid accidental overflow into the epidural space.[119]

For the RF procedure, the same viewing technique is used. The entry point is found by projecting the metal ruler over the caudal and posterior parts of the foramen. The cannula (SMK-C5 with a 2 mm exposed tip) is introduced parallel to the beam of the x-rays, and if necessary, the approach is corrected while still in the superficial layers until the cannula is projected on the screen as a single dot (Fig. 66.12). In practice, this dot should lie directly over the dorsal part of the intervertebral foramen at the transition between the middle and most caudal third. This dorsal position is chosen to avoid possible damage to the motor fibers of the segmental nerve and to the vertebral artery that runs anterior to the ventral part of the foramen. The direction of the x-rays is then changed to AP, and the cannula is further introduced until the tip is projected over the middle of the facetal column (Fig. 66.13).

The stylet is then replaced with the RF probe. After checking the impedance, electrical stimulation is started at a rate of 50 Hz. The patient should feel a tingling sensation between 0.4 and 0.65 V. The frequency is changed to 2 Hz, and the patient is observed for muscle contractions. These contractions should not occur below a voltage of 1.5 times the sensory threshold. Moreover, 0.5 mL of iohexol is injected to exclude accidental intradural positioning of the electrode, followed by 2 mL of 2% lidocaine. RF current is then passed through the electrode to increase the temperature of the tip to 67°C. This temperature is maintained for 60 s.

For the PRF procedure, the same technique is used. For the sensory stimulation, a sensation should be observed below 0.5 V. Since there are no reported complications, motor stimulation is unnecessary, nor is the use of contrast before the procedure.

• **Figure 66.12** Radiofrequency lesion adjacent to the dorsal root ganglion in a 20-degree oblique, 10-degree craniocaudal projection. The needle is positioned in the posterior aspect of the fossa at the junction of the middle and caudal third part. It is projected as a dot in tunnel vision.



• **Figure 66.13** Radiofrequency treatment of the dorsal root ganglion, anteroposterior view. The tip of the needle is projected over the facetal column.

Adverse Events and Complications

With conventional RF, a mild burning sensation (some deep neck soreness) in the treated dermatome is observed in 40%–60%, but it subsides spontaneously after one to three weeks.[132] Some sensory changes such as slight hypesthesia may occur but invariably disappear within three or four months.[15,16,119] With PRF-DRG, no sensory or motor complications were mentioned. A transient burning sensation may be felt.

Known complications of blockade of a cervical segmental nerve are epidural, intrathecal, or intravascular injection of local anesthetic. During this procedure, injectate can be placed in the adjacent venous plexus, in the vertebral artery, or even in the carotid artery. Because of the proximity of the higher cervical levels to the brain, there is a risk for local anesthetic CNS toxicity (seizure), although only a low volume of local anesthetic is used.[133]

Pulsed Radiofrequency Treatment of the Occipital Nerve

Occipital Neuralgia

The International Headache Society defines occipital neuralgia as paroxysmal shooting or stabbing pain in the dermatomes of the nervus occipitalis major or nervus occipitalis minor.[134] This definition was updated in 2013 to "unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution of the greater, lesser or third occipital nerves, sometimes accompanied by diminished sensation or dysesthesia in the affected area and commonly associated with tenderness over the involved nerve(s)."[135]

There are no epidemiologic data on occipital neuralgia. In 90% of the cases, the major occipital nerve is involved, compared to 10% involvement of the minor occipital nerve. In 8.7% of the cases, both occipital nerves are responsible for neuralgia.[136] Neuralgia is often caused by damage or irritation of the occipital nerves.

The course of the major occipital nerve is divided into three parts by two bends.[137] The major occipital nerve is formed by the dorsal ramus of the C2 nerve root. The first part runs between the origin of the nerve and the oblique capitis inferior muscle underneath which the nerve makes its first bend in a medial direction. The second part of the nerve runs cranially between the semispinalis capitis muscle on one side and the oblique capitis inferior, rectus capitis posterior, and the rectus capitis anterior muscles on the other side. When perforating the musculus semispinalis capitis muscle toward the surface, the nerve makes its second bend in a lateral direction. The third part of the nerve runs further laterally where the aponeurosis of the trapezius muscle is perforated, and the nerve begins its subcutaneous course. The major occipital nerve usually branches after perforating the aponeurosis.

Patients complain of a shooting or stabbing pain in the neck radiating over the cranium. Constant pain can persist between the paroxysms. The pain can be perceived in the retro-orbital area caused by the overlap of the C2 dorsal root and the nucleus trigeminus pars caudalis.[138] Vision impairment/ocular pain (67%), tinnitus (33%), dizziness (50%), nausea (50%), and congested nose (17%) can be present because of connections with cranial nerves VIII, IX, and X, and the cervical sympathicus.[139]

On clinical examination, hypo- or dysesthesia in the area of the nervus occipitalis major or minor and tenderness to pressure over the course of the nervus occipitalis major or minor can be observed. A positive Tinel's sign (pain upon percussion over the nerve) can be present.

Clinical presentation and a temporary improvement with a local anesthetic diagnostic block of the nervus occipitalis major and/or minor confirms the diagnosis.[134]

Evidence for Pulsed Radiofrequency Treatment of the Occipital Nerve

Following the GRADE system, there is very low evidence that PRF of the occipital nerves reduces occipital neuralgia.[51] In a prospective trial on 19 patients, 68.4%, 57.9%, and 52.6% reported an improvement of 50% or more one, two, and six months after PRF treatment of the occipital nerve, respectively. The mean visual analog score (VAS) score before treatment was 7.5 and declined to 3.5, 3.5, and 3.9 at one, two, and six months, respectively. There was a statistically significant improvement in the use of medication and quality of life parameters.[140,141]

In a case series of 10 patients with occipital neuralgia and a positive response to a greater occipital nerve (GON) and/or lesser occipital nerve (LON) block, fluoroscopy-guided GON and LON PRF were performed. The mean VAS score declined from 6.9 prediagnostic block to 1.2 and 0.8 post PRF and at the last follow up (mean 7.5 months), respectively. Eighty percent of the patients stopped the use of analgesics completely.[142]

A retrospective chart review included 102 patients with a primary diagnosis of ON who received PRF of the GON and the LON.[143] Fifty-one patients had a ≥50% pain reduction lasting for at least three months. Variables associated with a positive outcome included a traumatic inciting event (65.7% success rate; $P = 0.03$), lower diagnostic block volumes (odds ratio [OR]: 0.72; 95% confidence interval [CI]: 0.62–0.82), and multiple cycles of PRF (OR: 2.95; 95% CI: 1.77–4.92). Six "complications" were noted, five of which consisted of temporary worsening pain.

A randomized, double-blind, comparative-effectiveness study was published in 81 participants with ON or migraine with occipital nerve tenderness.[144] Forty-two participants were randomized to receive local anesthetic and saline, and three 120 second cycles of PRF per targeted nerve, and 39 were randomized to receive local anesthetic mixed with depot steroid and three rounds of sham PRF. Patients, treating physicians, and evaluators were blinded to interventions. The PRF group experienced a greater reduction in the primary outcome measure, average occipital pain at six weeks (mean change from baseline -2.74 +/- 2.49 vs. -1.38 +/- 2.0; $P < 0.001$), than the steroid group, which persisted through the six-month follow up. Comparable benefits favoring PRF were obtained for worst occipital pain through three months (mean change from baseline -1.93 +/- 3.20 vs. -0.54 +/- 2.64; $P = 0.043$), and average overall headache pain through six weeks (mean change from baseline -2.74 +/- 2.75 vs. -1.12 +/- 2.1; $P = 0.037$). Adverse events were similar between groups. No neurologic complications were reported.

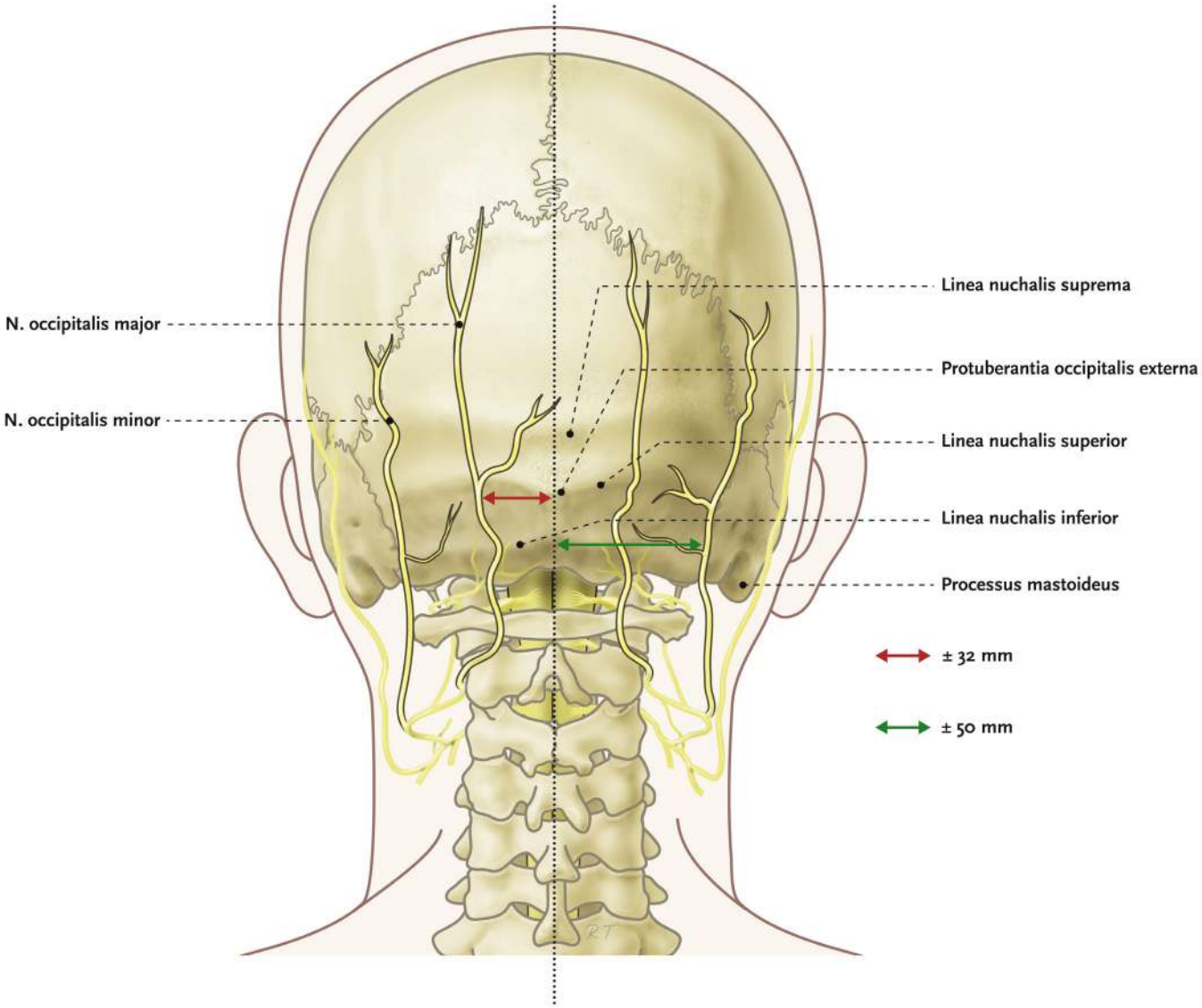
Technique for Pulsed Radiofrequency Treatment of the Occipital Nerve

The puncture site (22G needle, 5 cm, 1 cm active tip) is located according to the external landmarks described by Vital et al. (Fig. 66.14).[137] The thermocouple is introduced after perforation of the skin. The major and minor occipital nerves are located with a 50 Hz, 0.5 V current until the patient reports paresthesia in the dermatomes of the major and minor occipital nerve. Subsequently, a PRF treatment (45 V, 20 ms, 2 Hz) lasting 120 s with a maximum temperature of 42°C is performed twice.

Radiofrequency Treatment of the Lumbar DRG

Lumbosacral Radicular Pain

Several terms, including sciatica, ischia, nerve root entrapment, radicular pain, radiculopathy, and pain that goes down the leg, have been used to describe lumbosacral radicular pain. The latter and nerve root pain are more accurate and descriptive of the condition.[145,146]



In the general population older than 30 years old, up to 5% suffer from low back pain radiating into the leg,[147–149] making it probably the most commonly occurring form of neuropathic pain.[150–152] Acute lumbosacral radicular pain, caused by disc herniation and/or nerve root entrapment, improves considerably in the short term. About three-quarters of patients will recover after three months.[153–155] However, a high recurrence rate is reported.[156] Furthermore, when pain persists after this recovery period of three months, the prognosis of lumbosacral radicular pain is somewhat unfavorable, especially in the female population.[153,155,157–160] Patients suffering from lumbosacral radicular pain often experience a reduced functionality leading to an incapacity to work. A quarter of these patients are still out of work two years after onset.[161]

Lumbosacral radicular pain is characterized by radiating pain in one or more lumbar or sacral dermatomes; it may or may not be accompanied by paresthesia and/or symptoms of decreased function. The patient may experience the radiating pain as sharp, dull, piercing, throbbing, or burning. Pain caused by a herniated disc classically increases by sitting, coughing, or (excessive) stress on the lumbar discs and can be avoided by lying down or sometimes by walking.[147]

Conversely, pain from lumbar spinal canal stenosis typically increases walking and improves immediately upon bending forward.[162]

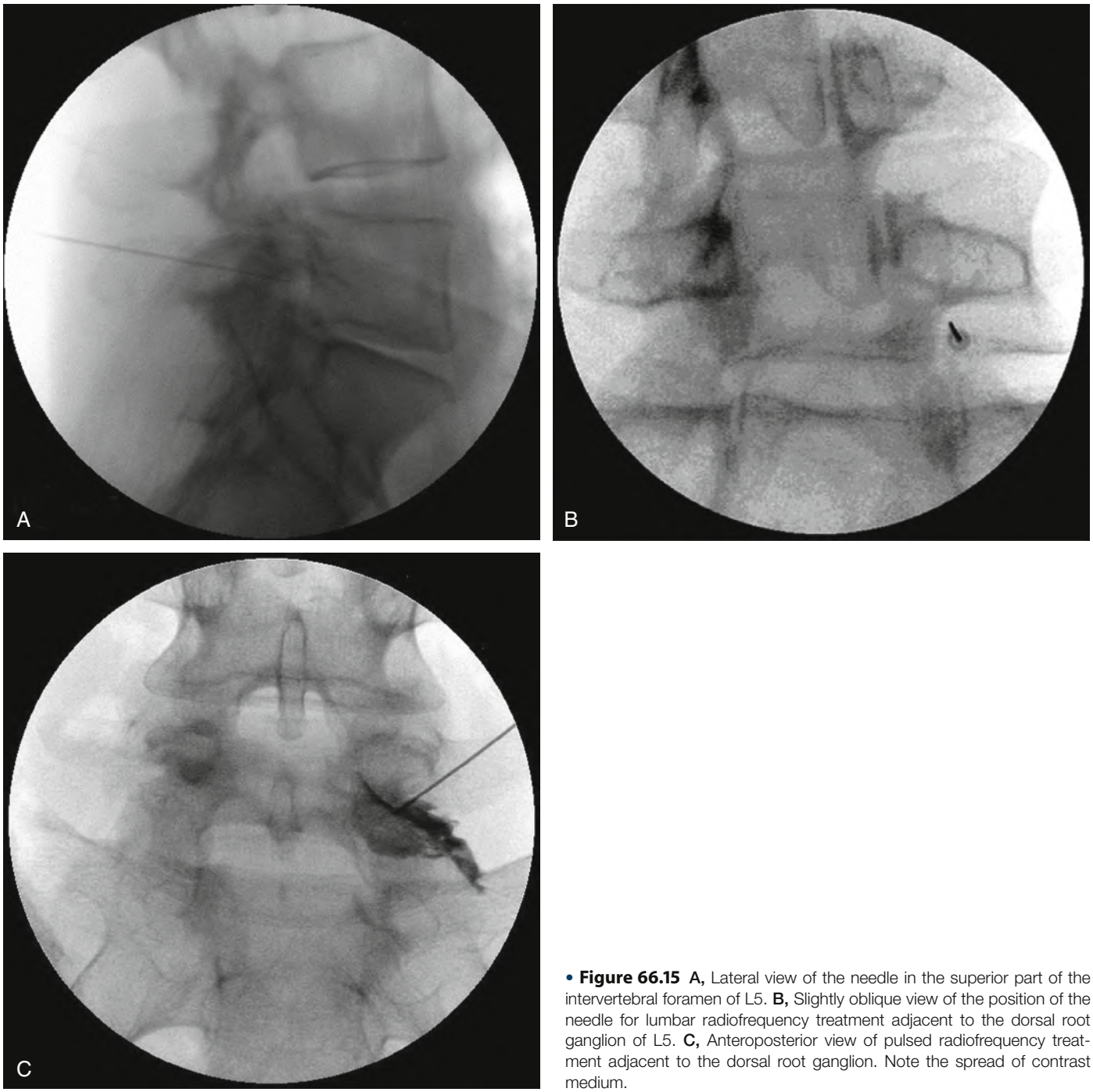
For clinical examination, the Lasègue/passive straight leg raising test was most often described and has a high sensitivity but low specificity. The crossed Lasègue test has good specificity but low sensitivity. Other neurologic signs such as paresis, sensory loss, or loss of reflexes are checked in a neurologic examination.[153,163] The suspected level is confirmed by imaging[164] and by one or more selective diagnostic blocks, using a minimal amount of local anesthetic.[165]

Procedure for Radiofrequency Treatment of the DRG

RF-DRG is aimed at creating a minimal lesion near the DRG for treating nerve root pain without causing neurologic deficits.[166] For this purpose, at the lumbar levels, a 10 cm electrode (22 gauge,

5 mm active tip) is placed in the dorsal cranial quadrant of the intervertebral foramen (lateral view) and introduced with its tip between a third and about halfway across the midfacetal column on the AP projection (Fig. 66.15).

Sensory and motor stimulation is applied at 50 and 2 Hz. The position of the electrode is adjusted if necessary to reach a sensory stimulation threshold of between 0.5 and 1.0 V. The motor stimulation threshold is required to be at least 1.5 times the sensory stimulation threshold. A final check of the electrode's position is made by injecting radiopaque contrast dye to visualize the nerve root and ganglion. Subsequently, a local anesthetic is injected through the cannula to achieve anesthesia. RF treatment is usually performed at 65°C–67°C for 90 s. At the sacral level, the position of the DRG is first visualized with a radiopaque contrast dye injected through a 22-gauge needle placed in the dorsal sacral foramen of the corresponding nerve root. Subsequently, a small hole is drilled with a Kirschner wire and a pneumatic drill through the overlying sacral bone to obtain access to the dorsal ganglion. The remainder of the procedure is identical to that at the lumbar level.



• **Figure 66.15** **A,** Lateral view of the needle in the superior part of the intervertebral foramen of L5. **B,** Slightly oblique view of the position of the needle for lumbar radiofrequency treatment adjacent to the dorsal root ganglion of L5. **C,** Anteroposterior view of pulsed radiofrequency treatment adjacent to the dorsal root ganglion. Note the spread of contrast medium.

Evidence for Radiofrequency Treatment of the DRG

Following the GRADE system, there is moderate evidence against the use of RF of the lumbar DRG.[51] In patients with radiating lower limb pain, one prospective[167] and several retrospective studies[10,168–171] reported beneficial effects of lumbosacral RF-DRG in 32%–76% of cases. In a retrospective study, 279 patients underwent RF-DRG because of chronic spinal pain radiating to the leg, and an initial success rate of approximately 60% was reported.[171] One high quality RCT to assess the efficacy of RF-DRG for lumbosacral radicular pain has been performed. In this study, lumbosacral RF-DRG failed to show an advantage over sham treatment with local anesthetics.[172] Since there is no clear evidence of the efficacy of continuous thermal RF-DRG treatment, the variable position of the lumbar DRG's and the potential to induce deafferentation pain, we prefer PRF-DRG.

Evidence for Pulsed Radiofrequency Treatment of the Lumbar DRG

Following the GRADE system, there is moderate evidence that PRF of the lumbar DRG reduces radicular pain.[51] The first RCT was a pilot study whose main aim was to consider the feasibility of assessing the efficacy of PRF-DRG compared to placebo.[173] However, this study was not powered for effectiveness.

An RCT (62 participants) compared the effect of three cycles of PRF treatment adjacent to the lumbar DRG (during the same session) with sham intervention in patients with MRI proven spinal canal stenosis. All participants also received a transforaminal epidural steroid injection after the PRF or sham procedure. Participants had ≥2-point pain reduction after a transforaminal epidural injection of local anesthetic and corticosteroid for a short duration (≤ six weeks). Patients in the PRF group showed a significantly greater improvement on a composite score for successful treatment during the three-month follow up than patients in the control group, but not on individual outcomes (mean difference pain reduction 0.331 (-0.252 to 0.914)), functional status, global perceived effect, and oral analgesic use.[174]

In another RCT (20 participants with lumbar radiculopathy) comparing pulsed radiofrequency (PRF) adjacent to the lumbar dorsal root ganglion (DRG) with transforaminal corticosteroid injections for patients with radicular pain, there were no differences in pain and functioning at two, four, eight, and 12 weeks.[175]

In another prospective RCT, 50 patients with lumbosacral radicular pain refractory to transforaminal epidural steroids received conventional monopolar or bipolar (two cannulae tips) PRF adjacent to the lumbar DRG. In the bipolar group, the pretreatment pain intensity (Numeric Rating Scale (NRS) 0–10) was 5.1±0.8. At one month, the mean NRS was 2.5±1.5, at two months, 2.6±1.6, and at three months, 2.6±1.7. In the monopolar PRF group, the mean NRS decreased from 4.6±0.8 pretreatment to 3.0±1.5 at one month, 3.0±1.5 at two months, and 3.0±1.5 at three months. Three months after treatment, 76% in the bipolar versus 48% in the monopolar PRF group reported successful pain relief (≥50% pain reduction).[176]

A prospective cohort study to evaluate the effect of PRF adjacent to the lumbar DRG on pain and quality of life included 65 patients with unilateral and monosegmental radiating pain. At six months follow up, the intention-to-treat analysis showed clinical success in 55.4% of the patients. The reduction in NRS and Oswestry Disability Index (ODI) was statistically significant compared to baseline. Moreover, the DN4 showed a significant improvement, indicating that the neuropathic component of the radicular pain is reduced after PRF treatment. The RAND-36 showed significant improvement in the physical component scale at three and six months.[177]

Procedure

The approach is identical to that described for RF-DRG. However, the threshold for sensory stimulation should be less than 0.5 V to reach the DRG maximally. Motor stimulation and the injection of dye are not necessary. If an adequate threshold is obtained, a pulsed current (routinely a 20 ms current and 480 ms without current) is applied for 4 min with an output of 45 V. During this procedure, the temperature at the tip of the electrode should not surpass 42°C.

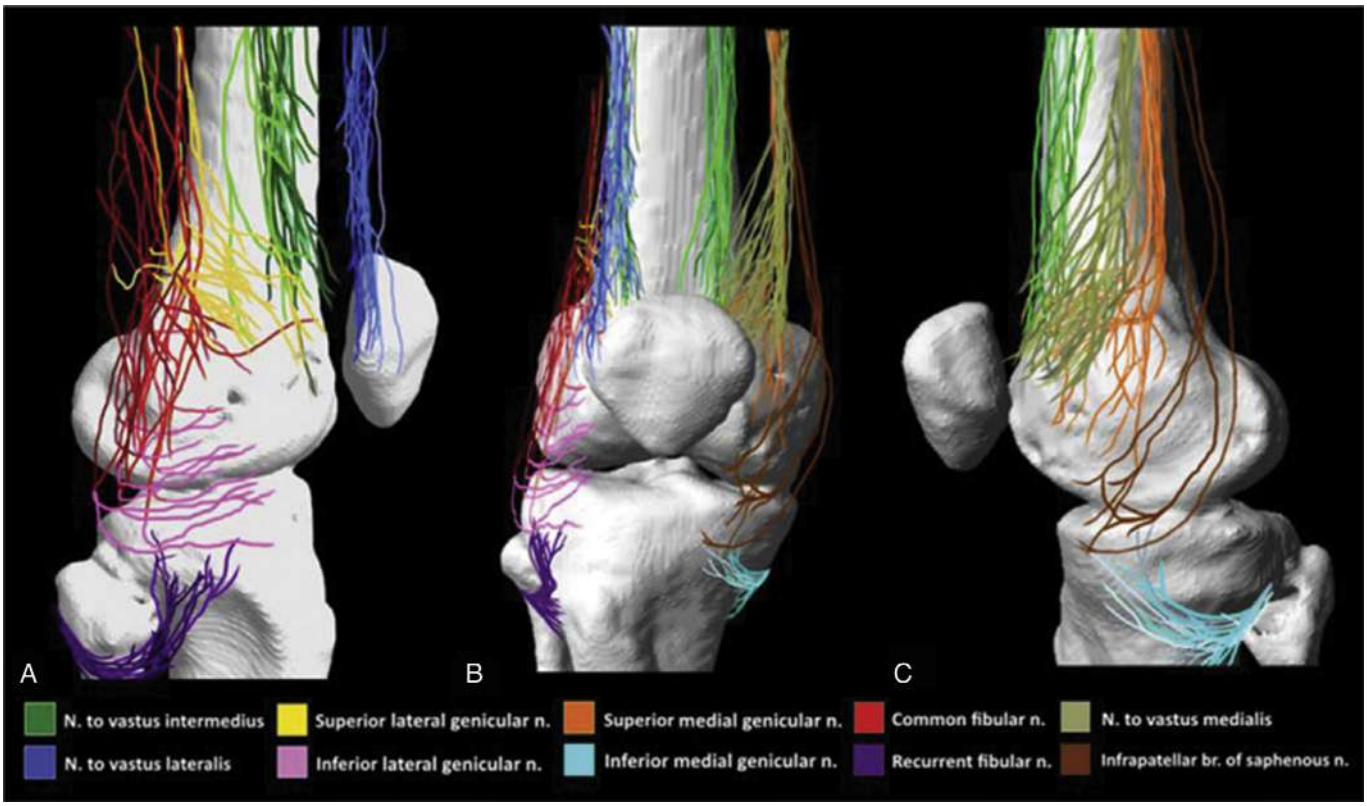
Radiofrequency Procedures on the Knee

Radiofrequency Treatment of the Genicular Nerves

Chronic Anterior Knee Pain

Chronic anterior knee pain is most frequently caused by osteoarthritis or because of a postoperative state. Knee osteoarthritis is a progressive degenerative process that affects joint cartilage and the subchondral bone. Approximately 10%–30% of all osteoarthritis patients suffer from disabling symptoms such as pain, stiffness, and loss of function, leading to psychological and sleeping disorders and a diminished quality of life.[178–181] When conservative treatment fails to treat the symptoms, a total knee arthroplasty can be performed.[182–185] Although not all patients are suitable candidates for a total knee arthroplasty procedure because of comorbidities or young age because of the limited lifetime of the prostheses used. In addition, the incidence of postoperative pain and functional limitation can mount up as high as 53%.[186–192] In those groups of patients, radiofrequency treatment of the genicular nerves can be an alternative treatment option. The sensory innervation of the anterior part of the knee is primarily accomplished by the genicular nerves. These are articular branches of the femoral, saphenous, obturator, common peroneal, tibial and sciatic nerves (Fig. 66.16). By targeting the superomedial, superolateral, and inferomedial genicular nerves, partial denervation of the anterior capsule of the knee can be achieved.[193–196]

Evidence. Radiofrequency treatment of the genicular nerves for pain because of *osteoarthritis* was first described by Choi and colleagues in 2011.[193] In this double-blind RCT, 38 elderly patients received a conventional RF treatment of 70°C for 90 s. They showed significant improvement in VAS, Oxford knee score, and global perceived effect at three months than placebo. Since this first report, multiple publications have investigated the effect of conventional and later pulsed and cooled RF treatment of the genicular nerves. In a recent systematic review and meta-analysis, which only included controlled trials, six studies were included, of which five studied a conventional and one a cooled radiofrequency treatment.[197] They concluded that a radiofrequency treatment showed significantly better short-term pain relief up to 24 weeks. The 50% pain relief rates at 12 and 24 weeks were also higher than the control group. The control group included sham operation, genicular nerve block, conventional analgesic therapy, and intraarticular knee injection. In terms of joint functional improvement, denervation therapy showed favorable outcomes at four and 12 weeks after treatment, but no significant difference was found at 24 weeks after the procedure between the groups. Overall, better results were reported in the radiofrequency treatment group with a relatively high grade of evidence. In another systematic review and meta-analysis on the effectiveness of RF treatment of the genicular



• **Figure 66.16** Frequency map of the innervation of the anterior knee joint. **A,** Lateral view. **B,** Anterior view. **C,** Medial view.

nerves, 12 RCTs were included.[198] They found that the VAS in the RF group were lower than those in the conservative treatment group up to three months (WMD -1.32, 95% CI -2.27 to -0.37, P < 0.01) after treatment, while there was no significant improvement in knee function. Furthermore, the authors concluded that radiofrequency ablation has better efficacy than pulsed radiofrequency treatment in reducing pain.[198] Recently, the results of a cooled RF treatment of the genicular nerves with a follow up to 24 months were published. They showed at least 50% pain reduction in 61% of the patients at 24 months.[199]

Studies on a radiofrequency treatment for *persistent post-surgery pain* (PPSP) after a total knee arthroplasty are less frequent. A large retrospective study showed no statistically significant difference between the outcomes after a conventional radiofrequency treatment in the group with PPSP and osteoarthritis.[200] Other observational studies also showed pain relief after (cooled) RF treatment.[201,202]

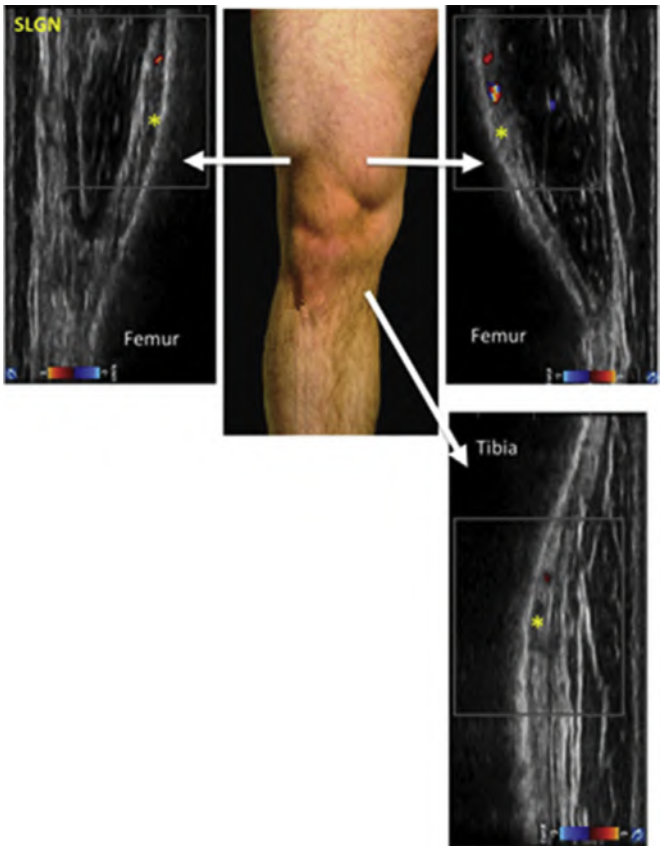
Procedure

The procedure was initially described under fluoroscopy and later on also with the use of ultrasound. Two RCTs compared fluoroscopy and ultrasound and found no differences in outcome.[203,204] Since there are no differences in outcome and ultrasound does not have radiation exposure and makes it possible to visualize soft tissue, ultrasound is the preferred imaging method to perform a radiofrequency treatment of the genicular nerves.

The patient is placed in a supine position with the index knee flexed 10–15° by placing a cushion in the popliteal fossa. The procedure is performed under sterile conditions. A diagnostic block can be performed, although there is a discussion on their utility since a recent study showed no prognostic value.[205] Using a high frequency linear ultrasound, the superomedial, superolateral, and inferomedial genicular nerves are targeted as described below. The inferolateral genicular nerve is not targeted because of its proximity to the common peroneal nerve with its motor branches (Fig. 66.17).[206]

Superomedial genicular nerve. The transducer is placed in a coronal orientation on the medial side of the proximal knee. After identifying the femoral medial epicondyle, the transducer is moved proximally and centered to the junction between the epiphysis and diaphysis of the femur and the vastus medialis superficial to it, just anterior to the adductor tubercle. The superomedial genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superomedial genicular artery is visualized just above the bony cortex, the target point is next to this artery. If the artery is not visualized, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer is turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 mL lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior "in plane" approach in the transverse plane until contact is made with the bony cortex at the center of the femur.

Inferomedial genicular nerve. The transducer is placed in a coronal orientation on the medial side of the distal knee to visualize the junction of the tibial medial epiphysis and diaphysis, the



• **Figure 66.17** Ultrasound probe position and corresponding images for genicular radiofrequency treatment. Color Doppler shows the corresponding genicular arteries. Treatment sites are marked with *yellow asterisks*.

inferomedial genicular artery, and the medial collateral ligament. Suppose the inferomedial genicular artery is visualized just above the bony cortex beneath the medial collateral ligament at the midpoint between the tibial medial epicondyle and the tibial insertion of the medial collateral ligament. In that case, the target point is next to this artery. If the artery is not visualized, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer was turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 mL lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior "in plane" approach in the transverse plane until contact is made with the bony cortex at the center of the tibia.

Superolateral genicular nerve. The transducer is placed in a coronal orientation on the lateral side of the proximal knee. After identifying the femoral lateral epicondyle, the transducer is moved proximally to visualize the junction between the epiphysis and diaphysis of the femur and the vastus lateralis superficial to it. The superolateral genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superolateral genicular artery is visualized just above the bony cortex, the target point is next to this artery. If the artery is not visualized, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer is turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 mL lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior "in plane" approach in the transverse plane until contact is made with the bony cortex at the center of the femur.

RF procedure. An RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produces paresthesia at a threshold of less than 0.5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches.

If the needle tip is confirmed to be in the correct position, 1 mL of lidocaine 2% is injected before the start of RF treatment. Typical RF treatment settings are 70–80° for 90 s, for cooled RF 60° for 150 s, and PRF 45 V for 4–8 min.

Adverse Events and Complications. Side effects are rare, and this minimally invasive procedure is considered safe. There are only five case reports of complications. Two articles reported a bleeding complication. The first article reported a peri- and intraarticular hematoma in three patients, two of whom were on anticoagulants.[207] Another article reported a periarticular hematoma in a patient.[208] In all cases, cooled RF of the genicular nerves was used, and bleeding was probably because of damage to the genicular arteries. There is a case report of septic arthritis and an injury to the pes anserine tendon after the use of cooled RF.[209,210] In the patient with septic arthritis, a steroid was injected after the radiofrequency treatment to reduce the risk of post-procedure neuritis and could have played a role. Finally, a case of a third-degree burn wound after the use of conventional RF is also published.[211]

Conclusions

RF treatment of chronic pain syndromes has seen a remarkable evolution over the past decade. RF current can now be applied in a continuous and pulsed fashion and application of continuous RF through an internally cooled electrode. Continuous thermal RF application method generates heat lesions. With cooled RF, the internal cooling of the electrode tip prevents excessive tissue heating, thus allowing the application of higher energy at lower impendency without creating scar tissue. The electrical field generated by PRF induces changes in nerve cells. Besides studies on efficacy and safety, computer modeling and *in vitro* and animal experiments have begun to shed light on the potential mode of action of PRF.

Evidence from good-quality studies demonstrates that continuous RF, cooled RF, and PRF can be applied to treat some chronic pain syndromes effectively. When performed in well-selected patients, who often suffer pain refractory to conventional treatment, the degree of pain relief can be higher than with conventional treatment. Moreover, in contrast to drug studies, the follow up period is much longer, providing proof of its long-term efficacy. RF treatment can produce minor, immediate side effects that typically resolve spontaneously within a short period. Major neurologic complications are rare but have been reported with conventional heat lesioning, not with PRF. Because of the low neurodestructive potential, PRF is our choice for treatment involving the DRG. These encouraging results point to the urgent need for further studies on this promising minimal neurodestructive mode of treatment. In future studies, attempts should be made to assess a homogeneous patient population with specific pathology.

Key Points

- Radiofrequency (RF) treatment consists of the application of a high frequency current by a needle to specific anatomic structures. RF current heats the tissue surrounding the tip of the needle. In interventional pain procedures, these small heat lesions cause selective denervation.
- Cooled RF, by utilizing an internally cooled electrode, allows increasing the lesion size without damaging the surrounding tissue.
- Pulsed RF (PRF) uses a high frequency current during 20 ms followed by a silent period of 480 ms, thus allowing the generated heat to be washed out. The effect is attributed to the creation of electric fields. Indications are neuropathic pain syndromes. Other indications are subject to research.
- An accepted indication for RF treatment of the head is trigeminal neuralgia (RF of the Gasserian ganglion). Neurologic evaluation is mandatory to exclude red flags for treatment. The first step in treatment is medication. RF treatment of the pterygopalatine ganglion can be used for cluster headaches and some atypical facial syndromes. PRF was studied for the treatment of trigeminal neuralgia. A recent development using high voltage PRF seems to prolong the treatment effect.
- Indications for RF treatment of the medial branches of the cervical facet joints include degenerative and posttraumatic neck pain. RF treatment of the (higher) cervical facet joints for cervicogenic headache awaits further research. RF of the facet joint is usually performed at two or three segmental levels since there is overlap in the innervation of the facet joints.
- Radicular pain in the upper extremity is caused by nerve root irritation. The involved spinal level can be estimated by the dermatome where the pain radiates and can be confirmed by diagnostic nerve root blocks. PRF treatment of the DRG is safer and has fewer side effects than RF treatment does.
- Lumbosacral radicular pain is probably the most frequent neuropathic pain. There is no clear evidence of the efficacy of continuous thermal RF treatment of the DRG and could potentially create a deafferentation pain. PRF treatment of the DRG is therefore preferred.
- Chronic knee pain because of osteoarthritis or persistent pain after knee arthroplasty can be treated with RF of the genicular nerves

Suggested Readings

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Pain Interventions for the Knee, Hip, and Shoulder

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Introduction

Targeted treatment of peripheral joint pain because of musculoskeletal disorders involves the utilization of intraarticular (IA) injections as well as ablative procedures. IA joint and bursa injections are used to treat pain in the joint and surrounding soft tissue structures. Radiofrequency ablation (RFA) creates a controlled lesion targeting sensory nerves associated with the large peripheral joints, including the hip, knee, and shoulder. Musculoskeletal system disorders, including osteoarthritis, are some of the most common medical conditions for which patients seek care. Musculoskeletal diseases are associated with high levels of disability, and significant economic costs.[1–3] Osteoarthritis is a non-inflammatory rheumatologic condition and the most prevalent form of arthritis. Osteoarthritis affects approximately 15% of the United States population and is the leading cause of lower limb disability among older adults.[4] The prevalence of osteoarthritis in the United States increased by 23% from 1990–2017, and the prevalence and incidence rates of osteoarthritis in the United States are among the highest in the world.[5]

Hollander first introduced IA corticosteroid injection for the treatment of rheumatoid arthritis (RA) in the 1950s.[6–8] The first clinical trial for IA joint injections for osteoarthritis was performed in 1958.[9] Currently, joint injections continue to be used extensively in a multimodal treatment platform for musculoskeletal conditions. The updated American College of Rheumatology (ACR) guidelines for the medical management of osteoarthritis strongly recommend IA injections and exercise and self-management programs to improve pain and function.[10]

Radiofrequency ablation for the management of osteoarthritic pain has evolved considerably over the last 20 years, and its use has expanded from the axial spine to peripheral joints. Thermal RFA has been well investigated and includes traditional monopolar and bipolar cannulae setups and internally cooled electrodes. Internally cooled electrodes create larger lesions with a significant portion of the lesioning occurring distal to the tip (i.e. approximately 40%), both of which are attractive for ablation of peripheral joint targets. Over the last 10 years, more research has been published demonstrating the effective employment of RFA for the management of painful osteoarthritis of the knee, hip, and shoulder, especially in individuals that have not responded to injectable corticosteroid therapy or viscosupplementation.[11]

This chapter provides an updated review of IA joint injections and RFA techniques targeting peripheral joints. Six major areas are covered: 1) pharmacology of common injectable agents, 2) indications for treatment, 3) image guided injection techniques, 4) IA injection-associated adverse effects and complications, 5) technique of RFA for treatment of peripheral joint pain, and 6) safety and effectiveness of RFA for peripheral joint pain. The three major joints addressed are the shoulder, hip, and knee. Assessments of the accuracy and therapeutic efficacy of each technique are provided.

Pharmacology of Agents Utilized for Joint Injections

IA needle placement is routinely used to deliver therapeutic agents to reduce pain and improve function. The three agents routinely employed for IA injections are local anesthetics, corticosteroids, and viscosupplements.

Local Anesthetics

Indications and Mechanism of Action

Local anesthetics are often utilized in combination with corticosteroids for IA and extra-articular injections. The rationale for utilizing LAs includes providing pain relief for the needle insertion itself and diagnostic purposes, as well as diluting and distributing the steroid preparation within the joint.

Local anesthetics act by reversibly binding to sodium channels on neuronal cell membranes, thereby blocking nerve conduction.[12] Local anesthetics also have transient anti-inflammatory effects and inhibit several leukocyte functions.[13]

Local anesthetics commonly employed for joint injections include the short-acting LA lidocaine and the long-acting LAs bupivacaine and ropivacaine.

Adverse Effects and Complications Associated With Local Anesthetic Injection

Local anesthetics are associated with local and systemic side effects. Local effects of LAs include myotoxicity and chondrotoxicity. Myotoxicity can occur from LA administration in or around muscle tissue, although it is usually not clinically relevant and muscle regeneration occurs.[14] Bupivacaine is more myotoxic than lidocaine and ropivacaine.[15] Local anesthetics produce myonecrosis through the lytic degeneration of the sarcoplasmic reticulum and mitochondria. The addition of corticosteroids to LA injection amplifies the muscle damage and prolongs the recovery phase.[16]

Myonecrosis rarely presents any clinically discernible manifestations in the course of routine use of local anesthetics for IA joint injections.

Local anesthetics are also chondrotoxic.[17–22] Most reported cases of chondrolysis occurred after the use of continuous IA local anesthetic infusions to manage postoperative pain rather than single IA injections.[21] *In vitro* studies have demonstrated that LAs cause mitochondrial dysfunction and apoptosis in human chondrocytes.[14] Chondrotoxic effects are influenced by the LA type and concentration. Grishko et al.[18] demonstrated that 2% lidocaine caused massive necrosis of cultured chondrocytes after 24 hours of exposure, whereas 1% lidocaine caused a detectable but insignificant decrease in cell viability. Therefore clinically, the use of lower concentrations of local anesthetic may be advantageous. For longer acting LAs, *in vitro* studies indicate that 0.5% ropivacaine is significantly less chondrotoxic to cultured human articular cartilage than 0.5% bupivacaine.[19] Similar to myotoxicity, combining LA with corticosteroids amplifies chondrotoxicity.[23] Although the molecular mechanisms of LA chondrotoxicity are still incompletely elucidated, LAs are thought to lead to mitochondrial dysfunction by influencing sodium, calcium, and potassium channels, ultimately resulting in cell necrosis or cell apoptosis in a time- and dose-dependent manner.[22]

When combining LA with corticosteroids, flocculation—aggregation of the particles of steroid—may occur.[24] Indeed, dilution with either saline or LA may influence the size of corticosteroid particles.[25] Betamethasone sodium phosphate/betamethasone acetate (Celestone Soluspan) should not be mixed with LAs that contain the excipients methylparaben, propylparaben, or phenol because of an increased risk of flocculation.[24] Flocculation leads to larger particles that may clog smaller bore needles, preventing injection. The effect of flocculation of the injected steroid on their therapeutic effect is unclear. Theoretically, the change in the size of the microaggregates of steroids could significantly alter the bioavailability of the steroid over time and the distribution within the joint after injection, altering their therapeutic effect.

Systemic effects of LAs include allergic reactions, central nervous system, and cardiac toxicity.[26] When appropriate steps are taken to avoid intravascular injection, including frequent aspiration and using small volumes for musculoskeletal injections, the incidence of these occurrences are low. Allergic reactions are more common with amino-ester LAs secondary to the production of metabolites related to para-aminobenzoic acid. Allergic reactions may also be because of the preservatives contained within the carrier solution (e.g. methylparaben). Cross-sensitivity does not exist between LA structural classes.

Corticosteroids

Indications and Mechanism of Action

Corticosteroids are often used for pain associated with symptomatic arthritis and soft tissue conditions, e.g. tendinitis, bursitis, and tenosynovitis. Numerous guidelines with a specific focus on osteoarthritis of the knee recommend IA corticosteroid injection for short-term pain relief.[27–30] Intraarticular steroid injections should be part of a multimodal treatment plan that includes aerobic and muscle-strengthening programs. Contraindications to IA injection are shown in Table 67.1.

The exact mechanism of action of corticosteroids in reducing arthritic joint pain has not been completely defined. Corticosteroids placed in the joint exert both local and systemic effects.[24,31,32]

TABLE 67.1 Absolute and Relative Contraindications for Intraarticular Joint Injections With Corticosteroids or Viscosupplementation

Absolute Contraindications
Overlying skin infection or recent procedure violating the epidermal layer (i.e. unhealed tattoo)
Fracture site
Severely compromised immune status
Suspected bacteremia
Suspected infectious arthritis
Hypersensitivity to previous viscosupplementation
Relative Contraindications
Coagulopathy
Hypersensitivity to avian products (proteins, feather, and egg products)[a]
Joint prosthesis
Poorly controlled diabetes mellitus
Previous lack of efficacy

[a]Consider using non-avian viscosupplementation products.

In individuals with RA, changes in the non-injected knee thermographic index, a quantitative measure of radiated energy from a defined area of the joint surface, have been demonstrated after IA prednisolone and triamcinolone hexacetonide (TH) injection into the symptomatic knee.[32,33] Intraarticular placement of methylprednisolone acetate (MPA), 40 or 80 mg, resulted in detectable systemic serum levels with peak levels occurring between 2 and 12 hours after injection. Additionally, endogenous serum cortisol levels were suppressed for up to one week after injection.[34] The systemic effects are further confirmed by the reduction of systemic inflammatory marker levels, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[24]

Corticosteroids have significant anti-inflammatory and immune effects and are active at the cellular level by combining with receptors to alter the rate of messenger ribonucleic acid synthesis and specific protein production. Specifically, corticosteroids result in increased synthesis of annexin-1 (lipocortin 1). Annexin-1 has phospholipase A_2-inhibitory activity that reduces the production of multiple inflammatory mediators, including eicosanoids, lysosomal enzymes, interleukin-1, leukotrienes, and prostaglandins.[35–37] The clinical response to IA steroids is accompanied by histologic improvement and decreased expression of genes involved in articular cartilage destruction.[38] Additionally, corticosteroids reduce microvascular permeability and synovial perfusion and increase synovial fluid viscosity.[39]

Corticosteroids seem to exert greater therapeutic effects with IA injection versus systemic or intramuscular (IM) administration. Injection of corticosteroid into multiple joints in RA patients resulted in greater improvement in ACR Criteria, patient disease activity, number of tender points, and reduced systemic side effects compared to equivalent IM dosing.[40] There is moderate evidence to support the effectiveness of IA steroid injections into the knee, with studies suggesting efficacy up to three months after injection.[41]

Corticosteroid Selection (Structure and Function)

The first steroid used for IA injection was hydrocortisone.[7,8] Pharmacologic developments have resulted in the advancement of steroid preparations over the past 50 years. However, substantial variation still exists for agent selection. There remains a paucity of randomized controlled trials (RCTs) comparing the efficacy of different corticosteroids for osteoarthritis. Thus evidence-based recommendations to guide steroid selection cannot be made. In 2014, a survey of ACR members indicated that agent selection for IA injections was usually determined empirically, and no consistent pattern was reported in terms of the type of corticosteroid based on anatomic site. The three most commonly utilized agents were MPA (used by 45% of respondents), triamcinolone acetonide (TA; 26.1%), and TH (22.1%).[42]

Table 67.2 lists commonly utilized corticosteroids that are FDA-certified for IA injection. TA extended release formulation is FDA-approved only for use in the knee joint and has not been studied in other peripheral joints. Approved for commercial use in the United States in 2017, it is supplied as a crystalline powder that is mixed at point-of-care with the manufacturer-supplied diluent to deliver 32 mg of TA extended release in 5 mL of solution that is equivalent to 40 mg of immediate-release TA. The extended release formulation utilizes poly (lactic-co-glycolic acid; PLGA) microspheres that allows for the slow release of TA. This formulation allows for the prolonged presence of steroids in the joint.[43] The only other corticosteroid approved for IA injection is dexamethasone. Dexamethasone, a highly water soluble, nonparticulate steroid preparation, exerts primarily systemic effects even after IA injection and is not routinely utilized for IA injections.[24,25] Ultimately, the selection of a depot corticosteroid can be based on cost and multiple pharmacologic properties, including solubility, crystal, and molecular structure.

Corticosteroid solubility may influence the duration of action, although published studies are conflicting. TH is the most insoluble injectable corticosteroid. Some IA injection studies have demonstrated a prolonged duration of activity with TH compared to other corticosteroids with higher solubility. Derendorf et al.[44] demonstrated that TH was associated with lower levels of systemic absorption and higher synovial levels than similar IA administration of TA. Comparison of TH and MPA for knee osteoarthritis did not support steroid solubility as the only factor influencing drug duration of action and therapeutic efficacy.[45] After three weeks, TH was more effective, but only MPA resulted in continued improvement in pain and disability scores at eight weeks. Another study comparing TH and MPA for RA treatment demonstrated a longer therapeutic effect with TH.[46] Thus available data are conflicting.

There is limited evidence to guide corticosteroid selection based on the peripheral joint target. MPA and TA seem to have similar short and intermediate term effectiveness for improving pain and function in peripheral joint targets. Most studies do not show greater pain improvement with a higher dose of steroids.[47]

The adverse effect profile of a corticosteroid should also be considered. Methylprednisolone acetate may be utilized for both joint and soft tissue injections, whereas TH is not recommended for soft tissue injections because of the higher risk of calcification, necrosis, and atrophy of soft tissues.[12,48,49]

Corticosteroid Dosing and Post-injection Protocols

Corticosteroid dosing ranges for various joints are listed in Table 67.2. Evidence-based recommendations for dosing and the maximum injection frequency do not exist. Cumulative doses of epidural steroid injections greater than 200 mg methylprednisolone equivalents annually have been shown to be associated

TABLE 67.2 Common Corticosteroid Preparations for Intraarticular and Periarticular Injections[19,28,30,33,40]

Preparation	Administration	Equivalent Dosage (mg)[a]	Anti-inflammatory Potency[b]	Solubility (%wt/vol)	Fluorinated	Dose Based on Joint Size
Betamethasone sodium phosphate/ betamethasone acetate (BSP/BA)	3 mg BSP/+ 3 mg BA per 1 mL	0.75	25	[c]Not specified	Yes	Large: 1–2 mL Medium: 0.5–1.0 mL Small: 0.25–0.5 mL
Methylprednisolone acetate (MPA)	20, 40, 80 mg/mL	4	5	0.001	No	Large: 20–80 mg Medium: 10–40 mg Small: 4–10 mg
Triamcinolone acetonide (TA)	10, 40 mg/mL	4	5	0.004	Yes	Large: 5–15 mg Small: 2.5–5 mg
Triamcinolone hexacetonide (TH)	5, 20 mg/mL	4	5	0.0002	Yes	Large: 10–20 mg Small: 2–6 mg
Triamcinolone acetonide (TA) extended release	32 mg powder for reconstitution	4	5	Insoluble[d]	Yes	Large: 32 mg[e]

[a]Equivalent to 5 mg prednisone. For TA and TH, the specific dosing for medium-sized joints was not mentioned.

[b]Relative potencies based on equivalent milligram doses with hydrocortisone being the relative baseline with a potency of one.

[c]The betamethasone preparation consists of the highly soluble ester BSP, which is devoid of particles and the less soluble BA.

[d]Per FDA labeling, the crystalline powder form of extended release TA is practically insoluble in water and very soluble in alcohol.

[e]The extended version of TA has been FDA-approved for use in the knee only and not in any other joint. The long-term safety and efficacy of repeated injections have not been studied.

with compromised bone mineral density,[50] and practitioners should be aware of the total steroid exposure a patient receives over time from all injection sources. Standard recommendations for weight bearing joints include a maximum of three to four injections per year, typically with three to four months between injections.[39,48] Conflicting evidence exists regarding the long-term safety of repeated IA corticosteroid injections. Long-term corticosteroid safety was studied by Raynauld et al.[51] in a randomized, double-blind placebo-controlled trial that compared IA knee injections of TA or saline every three months for up to two years. No detrimental effects or joint space destruction were observed on radiographs. Balch et al.[52] found no radiographic evidence of corticosteroid-induced joint destruction after long-term repeated IA injections (from four to 15 years) on knee joints affected by RA and osteoarthritis. However, a recent RCT examining IA corticosteroid injection treatment demonstrated significantly greater cartilage volume loss with no significant difference in pain scores with triamcinolone compared to saline when administered every three months over a two-year period.[53] Moreover, 80 mg of TA is not superior to 40 mg for IA knee injection in terms of pain relief or functional improvement.[54]

Following IA corticosteroid injection, patients are often advised to avoid overusing the joint for two to three days post-injection.[55] Studies investigating potential benefits of rest following corticosteroid injections have reported conflicting results.[24] Chakravarty et al.[56] demonstrated additional improvement in individuals that rested for 24 hours after IA injection, while Chatham et al.[57] found no benefit in individuals that rested for 48 hours.

If an individual is going to undergo a joint replacement surgery in the near future, caution should be exercised in performing IA injections close to the surgical date (typically within three months).[58] Retrospective comparative studies demonstrated an increased risk for deep infection in individuals that received IA corticosteroid injections shortly before the surgical replacement procedure.[59–61] However, Kokubun et al.[62] did not observe increased complications or infections IA injections within 90 days prior to total knee replacement. A meta-analysis in 2014 showed no clear association between IA injections performed prior to arthroplasty and the development of subsequent infection following joint replacement.[63] However, this study was not limited to injections performed within 90 days of surgery and thus speaks more to the apparent safety of injections performed at any time prior to arthroplasty. Patients should be counseled on the risks of periprosthetic infections when considering the use of IA injections as temporizing pain reduction techniques prior to joint replacement surgery.[64]

Adverse Effects and Complications Associated With Corticosteroid Injection

The adverse effects and complications of corticosteroid injections can be divided into local and systemic effects. Local adverse effects include tissue (skin or fat) atrophy, Nicolau's syndrome, tendon rupture, cartilage damage, post-injection flare, hemarthrosis, joint destruction, avascular necrosis, and septic arthritis.[12,48,65,66] Local tissue atrophy is one of the most common local adverse effects occurring in 1%–8% of cases and is often associated with superficial injection, inaccurate placement, and less soluble agents, e.g. triamcinolone compounds. Skin atrophy typically develops between one and four months after injection.[39,65] Methylprednisolone acetate is less frequently associated with soft tissue atrophy. Another common adverse effect is post-injection flare in pain, with a prevalence of 2%–25%. Post-injection flare typically presents within a few hours of injection and resolves within one to three days.[48]

Concern also exists for corticosteroid-specific effects on cartilage, tendon, and bone. Current data on corticosteroid effects on cartilage are conflicting. Animal studies have been inconsistent, with some demonstrating cartilage destruction while others revealing a cartilage-protective effect during acute inflammatory events.[67-73] Clinical studies suggest that cartilage loss may occur more frequently with repeated injections in large numbers.[12,53] Avascular necrosis has also been reported after joint injections, with the hip being the most commonly affected joint. This complication typically occurs after multiple joint injections within a short period and is seen more often in individuals who are concurrently taking oral steroids.[65] Tendon disruption has also occurred following corticosteroid injection, and care should be taken to avoid direct injection within tendons.[65,74]

Hemarthrosis and septic arthritis are two infrequent complications that carry significant morbidity. No specific guidelines exist for the performance of IA steroid injections in individuals on anticoagulants, and surveys have demonstrated substantial practice variation.[75] A small study demonstrated a low risk of hemorrhage in individuals taking warfarin sodium that received IA injections.[76] Septic arthritis has a reported incidence ranging from one in 3,000 to one in 50,000.[24,77,78] To reduce the risk of this adverse event, it is important to understand contraindications to injection (Table 67.1) and utilize a stringent aseptic technique. When performing a joint injection, if synovial fluid appears abnormal, the aspirated fluid should be sent for a complete white blood cell count (WBC) count, including differential, crystal analysis, Gram stain, and culture. Steroids should not be placed until the synovial fluid analysis (Table 67.3) is reviewed and interpreted. Septic arthritis is a medical emergency

TABLE 67.3 Synovial Fluid Analysis[231–233]

Diagnosis	Color	Clarity	WBC count per mm^3	% Neutrophils	Gram stain
Normal	Clear	Transparent	<200	<25	Negative
Non-inflammatory	Straw	Translucent	200–2000	<25	Negative
Inflammatory (Crystalline)	Yellow	Cloudy	2000–100,000	>50	Negative
Septic arthritis	Yellow	Cloudy	>25,000–50,000	>75	Variable
Pseudosepsis	NA	NA	5000–80,000[a]	NA	Negative

[a]Unlike septic arthritis, aspirate from joints with suspected pseudosepsis may contain an elevated eosinophil count suggestive of an immune-mediated inflammatory reaction.[82]

NA, Not available.

and can result in cartilage destruction, septicemia, and death within a few days if untreated. When septic arthritis is suspected, orthopedic surgery and infectious disease specialists should be consulted immediately. Arthrocentesis and synovial fluid analysis (Table 67.3) are mandatory for diagnosis and to guide treatment. Blood tests including a WBC, ESR, and CRP are neither sensitive nor specific in diagnosing or excluding septic arthritis.[79] Broad-spectrum antibiotics are initially started after obtaining the synovial fluid, and antibiotic selection is further guided by culture and sensitivity results. Septic arthritis has also been reported following viscosupplementation injections.[80]

Systemic adverse effects of IA corticosteroids include endocrine, metabolic, and vascular effects.[81] The most common and predictable endocrine effect is the rapid suppression of endogenous cortisol production. Maximal suppression of serum cortisol levels occurs 24–48 hours after IA injection. Adrenocorticotropic hormone (ACTH) levels typically return to normal between one and four weeks, indicating recovery of normal endogenous steroid production.[34,81,82] Metabolic effects include elevation of blood glucose levels in diabetic patients.[83] In people with diabetes with appropriate glucose control, acute hyperglycemia may persist for two to three days with peak glucose levels reaching 300 mg/dL.[81,84] Facial flushing is an unpleasant adverse effect seen in 15%–40% of patients.[12] The effect occurs, on average, 19 hours after injection and is self-limiting, lasting approximately 36 hours. Triamcinolone administration is associated with a higher rate of facial flushing.[81]

Viscosupplementation

Indications and Mechanism of Action

Viscosupplementation refers to IA administration of synthetic hyaluronic acid (HA). Intraarticular HA administration (IAHA) was initially recommended by numerous specialty guidelines, including the ACR, Osteoarthritis Research Society International (OARSI), and European League Against Rheumatism (EULAR), as a treatment option for the management of knee osteoarthritis.[27,85,86] Expert consensus supported the use of IAHA as an effective treatment in mild to moderate knee OA and is a well tolerated treatment in the knee and other joints.[87] However, the 2019 ACR and Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee continued to strongly recommend the utilization of intraarticular glucocorticoid injections but changed their position on intraarticular HA injections. The 2019 recommendations conditionally recommended against the use of intraarticular HA injections in individuals with osteoarthritis of the knee and strongly recommended against its use in patients with hip osteoarthritis.[10] The guidelines concluded that the initial recommendation for IA HA injections did not consider the risk of bias of individual primary studies. The studies that demonstrated benefit were often restricted to studies with a higher risk of bias. When meta-analyses were limited to trials with a low risk of bias, the effect size of HA injections compared to saline was not statistically significant. Therefore careful risk-benefit assessment and patient and physician informed decision making is required before performing IA viscosupplementation for the knee

IA HA administration is approved by the United States Food and Drug Administration (FDA) only for knee osteoarthritis. Off-label application of IAHA has been reported for the shoulder, hip, and ankle. Selection criteria include failure of standard noninvasive treatment programs with clinical and radiologic signs of knee osteoarthritis.[27,88] Osteoarthritis severity may be an important predictor in determining the magnitude of clinical response to IAHA injection. In general, IAHA seems most beneficial in individuals with early osteoarthritis and radiographic evidence of joint space preservation.[89–91] Contraindications to IAHA injection are shown in Table 67.1.

Although the exact mechanism of action is unknown, the treatment goal is to restore the viscoelastic properties of synovial fluid.[92] Observed treatment benefits are not entirely explained by IA residence time, which is considerably shorter than the duration of clinical benefit. Several *in vitro* and pre-clinical studies have proposed additional mechanisms of action for IAHA, including inhibition of inflammation and cartilage degradation, reduction of pain mediators, and induction of *in vivo* HA synthesis.[93,94] HA has been best studied in the knee; some studies show that it may provide longer lasting improvement in pain and function than intra-articular steroid (IAS).[95]

Viscosupplementation Agent Selection (Structure and Function)

HA is a glycosaminoglycan synthesized by synoviocytes, fibroblasts, and chondrocytes that confers viscous and elastic properties to the joint.[96] Viscosupplementation formulations differ in their origin, production method, molecular weight, treatment schedule, and physicochemical properties.[94] At least 12 HA preparations are approved for knee osteoarthritis in the United States, initially offered as a series of injections with the first single injection option introduced in 2009.[96] Formulations are classified as cross-linked or non-cross-linked and are further defined by chemical modifications and production method (avian- versus non-avian-derived products). Non-avian products are produced by bacterial fermentation. All available avian preparations are derived from rooster combs and are purified natural products. The avian sourced hylan G-F 20, Gel-One®, and non-avian sourced Monovisc®, Durolane® are chemically modified (cross-linked HA) to increase the molecular weight to replicate the properties of native synovial fluid more closely and to lengthen IA residence half-life.[92,97] No conclusive evidence exists that differences in viscosupplement physical properties translate into superior clinical efficacy.[98]

Dosing and Post-injection Protocols

The recommended dosing regimens for specific viscosupplementation products are based on the physical properties and the manufacturers' prescribing recommendations. Currently, there is insufficient evidence to guide the appropriate injection frequency and dosing intervals. Common recommendations are either for a single injection or a total of two to five weekly injections based on the selected product (Table 67.4), but these are solely based on the manufacturer's recommendations that arose from the pre-marketing registry trials for each product.[99] Evidence-based recommendations do not exist for interval timing for repeating treatment, although repeated courses of IAHA are generally safe and well tolerated, with injections or series spaced at least six months apart demonstrating effectiveness in several RCTs.[100] Insurance providers typically require a minimum of 6 months between repeated treatment courses. Pre-injection synovial fluid aspiration and avoidance of excessive weight bearing activities for 48–72 hours post-injection may yield better outcomes.[89,91,101]

Adverse Effects and Complications Associated With Viscosupplementation Injection

In general, viscosupplementation is well tolerated with more local reactions but fewer systemic side effects than other medical interventions for managing knee osteoarthritis.[102] Frequently reported

TABLE 67.4 Commonly Used Hyaluronic Acid Preparations for IA Viscosupplementation

Product Structure	Product Name	Origin	Molecular Weight (kDa)	Injection Interval	Dosing Volume	Recommended Dosing Regimen[a]
Cross-linked	Synvisc®	Sodium Hyaluronate	6000	One week	2 mL	3
	Synvisc-One®	Sodium Hyaluronate	6000	N/A	6 mL	Once
	Gel-One®	Sodium Hyaluronate	NA	NA	3 mL	Once
	Monovisc®	Bacterial fermentation (Non-avian)	1000–2900	NA	5 mL (3-injection Orthovisc®)	Once
	Durolane®	Bacterial fermentation (Non-avian)	NA	NA	3 mL	Once
Non-cross-linked	Supartz®	Sodium Hyaluronate (Naturally- derived)	620–1170	One week	2.5 mL	3 or 5[a]
	Hyalgan®	Sodium Hyaluronate (Naturally- derived)	500–730	One week	2 mL	3 or 5[a]
	Visco-3™	Sodium Hyaluronate (Naturally- derived)	620–1170	One week	2.5	3
	Orthovisc®	Bacterial fermentation (Non-avian)	1000–2900	One week	2 mL	3-4[a]
	Euflexxa®	Bacterial fermentation (Non-avian)	2400–3600	One week	2 mL	3
	GelSyn-3™	Bacterial fermentation (Non-avian)	1100	One week	2 mL	3
	GenVisc® 850	Bacterial fermentation (Non-avian)	620–1170	One week	2.5 mL	5
	TriVisc™	Bacterial fermentation (Non-avian)	620–1170	One week	3 mL	3
	Hymovis®	Bacterial fermentation (Non-avian)	NA	One week	3 mL	2

[a]Treatment schedule: Please refer to manufacturers' specific recommendations.

kDa, Kilodalton; *N/A*, not applicable

local adverse effects include injection site pain, short term erythema, and joint effusion development. These effects are typically mild and resolve within 24–48 hours.

Other infrequent local adverse effects include pseudosepsis and pseudogout.[103] Pseudosepsis, a severe acute inflammatory reaction, is considered an extreme local adverse reaction. It is characterized by a large effusion, severe pain, and cellular infiltration occurring within 24–72 hours after the injection. Pseudosepsis often requires clinical intervention such as arthrocentesis, IA corticosteroids, and systemic analgesics.[104] Pseudosepsis may be misdiagnosed as septic arthritis.[104] The proposed mechanisms of pseudosepsis include an immune reaction to cross-linked products. Inappropriate injectate placement has also been suggested as a causative factor in pseudosepsis.[89,105] When pseudosepsis is suspected, other clinical conditions such as septic arthritis must be ruled out.

Pseudogout is a type of crystal-induced arthropathy characterized by calcium pyrophosphate crystal deposition. Individuals with pseudogout present with acute pain, joint swelling, and decreased function. The pathophysiology leading to pseudogout after IAHA is not clearly understood. Pseudogout occurs more frequently in patients with preexisting chondrocalcinosis. Therefore IAHA should be used with caution in these individuals.[106,107] Pseudogout may also be mislabeled as pseudosepsis. Synovial fluid analysis is helpful in making the correct diagnosis (Table 67.3).

Joint Injection Techniques

Three injection techniques (palpation, ultrasound guided, and fluoroscopy guided) may be used for the placement of drugs into the IA space. The use of ultrasound improves both accuracy and short term outcomes in pain and function compared to palpation guidance with IA injections.[108] Palpation guided IA injections are associated with inappropriate needle placement rates as high as 50%–60%.[109,110] Fluoroscopy and ultrasound guided methods have evolved to increase injection accuracy. Although both techniques allow for needle visualization, ultrasound guidance has advantages. Benefits of ultrasound guided injection include dynamic real-time multiplanar imaging of relevant anatomic structures, direct visualization of injected therapeutic agents, and the absence of ionizing radiation.

Improved injection accuracy with visually guided techniques ensures correct IA compound placement and may significantly

influence clinical outcomes. The benefit of accurate IA placement was demonstrated in a randomized control trial evaluating clinical outcomes in individuals who received either anatomic palpation guided or ultrasound guided IA joint injections.[110] A total of 148 joint injection procedures were studied, with 95% of injections occurring in large joints (knee, hip, shoulder, elbow, wrist, and ankle). The remaining 5% of the injections occurred in small joints (interphalangeal or metacarpophalangeal joints). IA knee injections represented the largest category at 42%. Sonographic needle guidance was found to be statistically superior in multiple areas. Compared to palpation guided injections, ultrasound guided injections resulted in a 43% reduction in procedural pain, a 58.5% reduction in absolute pain scores at two weeks, a 26% increase in responder rate, and a 62% reduction in the non-responder rate. Sonographic needle placement also improved detection of joint effusion by 200% and increased aspirated fluid volume by 337%. The authors concluded that sonographic guidance for IA injections is associated with significant short-term clinical advantages.

This section will describe the injection techniques for the three major joints: shoulder, hip, and knee. Emphasis will be placed on the image guided techniques. The efficacy for IA and viscosupplementation will also be discussed. Strict aseptic technique should be utilized for all injections.

Shoulder

Anatomy

The shoulder is a complex anatomic structure allowing multidirectional movement. The shoulder girdle refers to several articulations associated with important muscle groups that provide a wide range of shoulder movement. Three important shoulder joints are the glenohumeral, acromioclavicular, and sternoclavicular. The glenohumeral joint is a ball and socket joint that allows abduction, adduction, flexion, extension, rotation, and circumduction. The acromioclavicular joint is situated superficially between the lateral end of the clavicle and the acromion process of the scapula. The rotator cuff muscles include the supraspinatus, infraspinatus, teres minor, and subscapularis. The subacromial bursa is positioned within the subacromial space between the overlying deltoid muscle and the underlying supraspinatus tendon and provides rotator cuff lubrication.

Injection techniques for the shoulder including palpation (anatomic landmarks) and image guided (ultrasound and fluoroscopy) approaches. We will focus the discussion on image guided techniques for the three major anatomic locations for shoulder injections: 1) subacromial/subdeltoid bursa, 2) glenohumeral joint, and 3) acromioclavicular (AC) joint. Shoulder injection using only anatomical landmarks may be inaccurate,[111–115] which may adversely affect short-term clinical outcomes.[116,117]

Subacromial/Subdeltoid Bursa Injections

Indications and Musculoskeletal Pathophysiology

Subacromial injections are used to treat various shoulder conditions, including rotator cuff pathology, subacromial bursitis, and subacromial impingement.[118,119] Impingement refers to the narrowing of space available for the rotator cuff resulting in compression of rotator cuff tendons against the undersurface of the coracoacromial arch.[120] Rotator cuff impingement may result in the development of bursitis, subacromial inflammation, secondary tendinitis, and degenerative tears.[121]

Clinical outcomes following subacromial injections have been linked to the accuracy of injection, the severity of imaging findings, and the duration of symptoms.[116,117,122] Specifically, an MRI finding of isolated bursitis without rotator cuff tear, younger age, and shorter duration of symptoms (less than one year) are associated with better post-injection clinical outcomes.[122] Outcomes are typically better when injection therapy is combined with an appropriate home exercise program.[123]

Palpation Guided Anatomic Injection Technique

Commonly utilized portals for palpation guided subacromial injections include the posterior lateral and anterior-lateral approaches.[111,121,124,125] In the posterior approach, the needle is inserted 1–2 cm inferior to the posterior lateral aspect of the acromion process. The needle is directed anteriorly and cephalad. In the anterior approach, the needle is inserted approximately 1 cm inferior to the anterior/inferior aspect of the acromion process. The needle is directed posteriorly and cephalad. The posterolateral approach is preferred because of the existence of a larger subacromial space, although no definitive evidence exists to support the superiority of any single approach.[125]

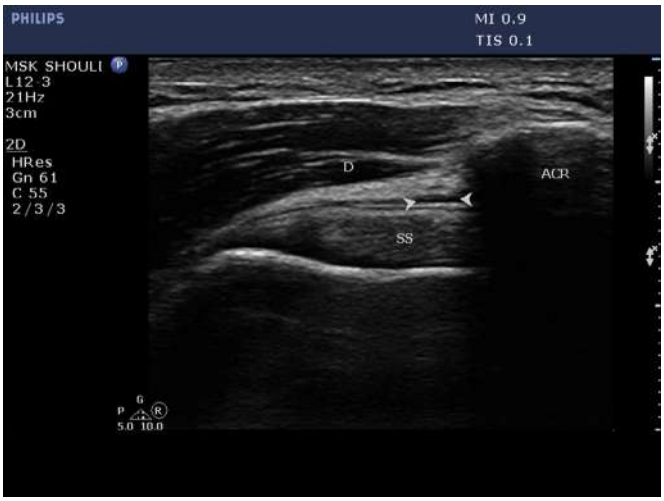
Fluoroscopy Guided Injection Technique

Limited information exists detailing subacromial joint injections performed under fluoroscopic guidance. The utilization of fluoroscopy with radiographic contrast IA injection has been employed as a confirmatory adjunct to palpation guided injections to ensure appropriate needle and injectate placement.[124,126]

Ultrasound Guided Injection Technique

The patient sits in the upright position with the shoulder extended, elbow flexed, and palm of the hand placed over the ipsilateral back pocket (modified Crass position).[119,127] Initially, the IA portion of the biceps tendon is identified over the anterior shoulder with a high frequency linear-array ultrasound probe. The probe is oriented in the coronal plane and is moved superiorly and posteriorly until it is aligned with the supraspinatus tendon longitudinal axis. The supraspinatus tendon in this position has a typical beak-shaped appearance.[127] The subacromial-subdeltoid bursa is visualized as a thin hypoechoic band outlined by highly reflective lines corresponding to peribursal fat between the deltoid muscle and supraspinatus tendon (Fig. 67.1).[119,128] Other structures visualized include the acromion process at the medial end and the greater tuberosity at the lateral end of the scan plane. The lateral end of the transducer is marked for the skin entry. A procedure needle is advanced with an in-plane technique into the subacromial-subdeltoid bursa. After confirming the needle position within the bursa, the desired medication is injected slowly while noting the expansion of the bursa.[129] Injection without bursa distention suggests intramuscular or intratendinous needle insertion and requires needle tip repositioning. The technique can also be performed with the patient in the lateral recumbent position on the contralateral shoulder with the targeted extremity extended and relaxed along the torso, and target approached using an in-plane technique using the same landmarks as described above.[130]

When directly comparing visually guided techniques to palpation guided techniques, Naredo et al.[117] demonstrated improved technique accuracy and outcomes (functional shoulder assessment) with ultrasound guided injection versus palpation guided injection. Palpation guided injection resulted in a 30% accuracy rate when validated with ultrasound confirmation of injectate placement. Image guided injections are shown to be more accurate



• **Figure 67.1** Ultrasound view of the subacromial-subdeltoid bursa along the long axis of the supraspinatus tendon. *Asterisks (*)* indicate peribursal fat; *arrowheads* identify the subacromial bursa. *ACR,* Acromion process; *D,* deltoid; *H,* humerus; *SS,* supraspinatus tendon. (Please see text for a detailed description of patient and ultrasound probe positioning.)

• **Figure 67.2** Glenohumeral joint visualization by fluoroscopy. The posterior aspect of the glenohumeral joint space is viewed tangentially under fluoroscopic guidance. The inferomedial quadrant of the humeral head is marked *(arrowhead)* as the needle entry site. (Please see text for a detailed description of patient positioning.)

than palpation guided injections.[131] When examining individual studies for palpation guided anatomic injection techniques, clinical and cadaveric studies have reported variable accuracy rates in the range of 29%–91%.[111,116,124,126,132,133] Improved injection accuracy resulting from ultrasound guidance[117] or fluoroscopic confirmation[116] may positively affect short-term clinical outcomes.

Mathews et al.[134] questioned the reliability of fluoroscopy guided injections in a cadaveric study. Approximately 7% of injections considered to be accurately placed under fluoroscopic guidance were found to be placed inaccurately on subsequent cadaveric dissection. Because of the complex soft tissue anatomic structures of the shoulder joint, fluoroscopic guidance may not guarantee accurate needle placement in the subacromial space. Better visualization of soft tissues using ultrasound guidance potentially favors this method for subacromial joint injections and diagnostic shoulder imaging.[117,121,127]

Glenohumeral Joint Injections

Indications and Musculoskeletal Pathology

Glenohumeral joint injections are used as a non-operative management technique for painful glenohumeral arthrosis or adhesive capsulitis (frozen shoulder).[118]

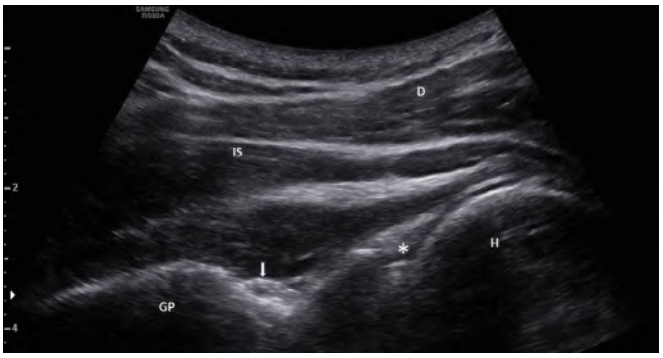
Fluoroscopy Guided Injection Technique

The patient is placed in the lateral decubitus position with the head resting on the non-targeted arm with the targeted shoulder in the non-dependent position. A bolster is placed in front of the patient, and then the patient rotates onto the bolster with the targeted arm internally rotated until the glenohumeral joint space is aligned under the fluoroscopic anterior-posterior view (Fig. 67.2).[135] The skin entry site is marked over the inferomedial quadrant of the humeral head.[136] A 22-gauge needle is advanced with a coaxial fluoroscopy guided technique to the humeral head. After negative aspiration, radiographic contrast is injected to confirm IA needle placement. Although the posterior approach is commonly used, additional fluoroscopic techniques have been described utilizing the anterior[137] and rotator cuff interval approaches.[138]

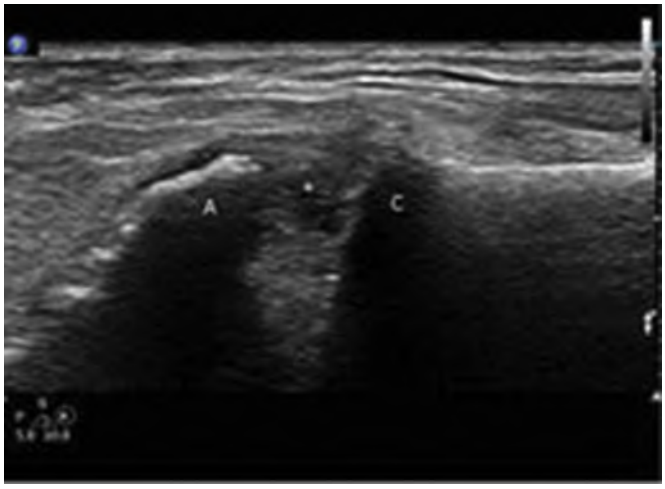
Ultrasound Guided Injection Technique

The patient is placed in either the semi-prone position resting on the contralateral shoulder or in an upright sitting position with the ipsilateral arm placed on the contralateral shoulder to open up the glenohumeral joint space.[112] A high frequency linear-array probe facilitates visualization of superficial structures, including the infraspinatus muscle, glenoid cavity, glenohumeral joint, and associated labrum. Many patients may require the use of a curvilinear probe depending on body habitus. The probe is positioned over the infraspinatus fossa inferior and parallel to the scapular spine. The field of view is adjusted to encompass the posterior glenoid rim and the glenohumeral junction (Fig. 67.3). The posterior glenoid labrum appears as a triangular structure. The lateral end of the transducer is marked for the skin entry. A 22-gauge needle is advanced with an in-plane approach into the joint deep to the infraspinatus tendon, between the posterior glenoid labrum and the hypoechoic humeral articular cartilage.[139] Resistance at the time of injection suggests a needle tip position within articular cartilage or labrum and necessitates needle repositioning. Alternative techniques include the anterior[140] and rotator cuff interval approaches.[141] There is no statistically significant difference in terms of the accuracy of GH joint injection between fluoroscopic and ultrasound guidance, and sparing the patient radiation exposure may be a consideration when selecting guidance modality.[142]

When directly comparing ultrasound guided techniques to palpation guided techniques, Cunnington et al.[143] demonstrated that junior trainees with basic ultrasound skills achieved higher IA injection accuracy rates using ultrasound guided (63%) than using palpation guided (40%) approach. No studies exist that directly compare fluoroscopy versus palpation guided glenohumeral injection techniques. In one review, image guidance (fluoroscopy, ultrasound, and MRI) had an average accuracy rate of 95%



• **Figure 67.3** Glenohumeral joint visualization by ultrasound. The posterior aspect of the glenohumeral joint space is viewed using ultrasound guidance. *Asterisk (*)* indicates the Glenoid labrum. *D,* Deltoid; *IS,* infraspinatus; *GP,* glenoid process; *downward block arrow,* spinoglenoid notch; *H,* humerus. (Please see text for a detailed description of patient and ultrasound probe positioning.)



• **Figure 67.4** Ultrasound view of the acromioclavicular joint. *Asterisk (*)* indicates the acromioclavicular joint. *C,* Clavicle; *A,* acromion. (Please see text for a detailed description of patient and ultrasound probe positioning.)

compared to an average accuracy rate of 79% with palpation guidance.[131] When examining individual studies for palpation guided anatomic injection techniques, clinical and cadaveric studies have reported variable glenohumeral injection accuracy rates in the range of 27%–100%.[116,133,144–146]

Improved glenohumeral injection accuracy resulting from ultrasound guidance[143,147] or fluoroscopic confirmation[116,143] significantly enhances the short-term clinical outcome. Sibbitt et al.[110] demonstrated in a study involving multi-joint interventions that ultrasound guidance significantly improves clinical outcomes. When directly comparing ultrasound guidance with fluoroscopic guidance, Rutten et al.[112] demonstrated that ultrasound guidance improved procedural outcomes. Ultrasound guidance resulted in a first pass accuracy rate of 94% compared to 72% obtained with fluoroscopic guidance, and also comparatively reduced procedural time and patient discomfort levels.

Acromioclavicular Joint Injection

Indications and Musculoskeletal Pathology

Acromioclavicular (AC) joint injections are employed for diagnostic and therapeutic purposes for painful AC joint arthritis.[118,148]

Fluoroscopy Guided Injection Technique

Few reports exist describing fluoroscopically guided AC joint injections. With the patient in the supine position, a 25-gauge needle is advanced into the AC joint using either an anterior or superior approach. Less than 0.5 mL of radiographic contrast is utilized to confirm IA placement.[149,150]

Ultrasound Guided Injection Technique

Ultrasound guidance has been associated with greater improvement in pain and function than palpation guided approaches to AC joint injection.[151] The accuracy rate of intraarticular AC joint injection using palpation guidance has been shown to be only 36.5%.[152] Both in-plane[153] and out-of-plane[119,129,154] ultrasound guided techniques have been described. However, the out-of-plane technique is preferred because of this joint's small size and superficial location. The patient is positioned in the sitting position, and a high frequency linear-array probe is placed in an anatomical coronal plane over the superficially located AC joint (Fig. 67.4). The acromion process, clavicle, joint capsule, and wedge-shaped fibrocartilaginous disk are visualized. A 25-gauge needle is advanced using an out-of-plane technique. Because of the shallow AC joint depth, needle insertion must be carefully controlled to avoid misplacement into the subacromial space.[119,148]

Because of the small size and variable morphology of the AC joint, intraarticular needle placement without image guidance is often difficult and inaccurate.[132,155] In a direct comparison cadaveric study, ultrasound guided AC injections using the in-plane technique demonstrated a 100% accuracy rate compared with the 40% accuracy rate for palpation guided injections.[153] For anatomically guided palpation techniques, clinical and cadaveric studies have reported variable accuracy rates in the range of 40%–66% when confirmation of needle or injectate placement was validated with fluoroscopy or cadaveric dissection.[132,155,156] Sabeti-Aschraf et al.[154] observed similar clinical outcomes following palpation guided and ultrasound guided AC injections when performed by experienced physicians.

Efficacy of Shoulder Injections

Efficacy of Subacromial/Subdeltoid Bursa Injections

Evidence for the efficacy of subacromial/subdeltoid bursa injections is conflicting. This incongruity may correlate with the lack of selection of specific shoulder diagnoses in some study populations or inaccurate injectate placement.[117,122,157] Predictors of success following subacromial injections have been investigated. MRI findings consistent with low-grade impingement and bursitis without evidence of a rotator cuff tear are positive predictors of injection response.[122] The use of image guidance may improve the effectiveness of subacromial/subdeltoid bursa injections in terms of pain, function, and range of motion.[158]

Efficacy of Glenohumeral Joint Injections

The majority of available evidence for therapeutic glenohumeral joint injection relates to adhesive capsulitis.[157] Multiple systematic reviews have demonstrated that IA corticosteroid injection for the treatment of adhesive capsulitis may result in improvement in function and range of motion, particularly when performed in conjunction with physical therapy and exercise,[159–161] with the most recent systematic review suggesting that improvements in range of motion may be sustained for a longer period (24 weeks) than pain relief (eight weeks). IA GH joint injection is considered

to be as effective as physical therapy for the treatment of adhesive capsulitis with neither demonstrating clear superiority across nine RCTs and certainly a reasonable approach would be to incorporate both into a comprehensive nonsurgical management program.[162] IA GH joint injections may also be considered for standard conservative treatment of painful GH joint arthritis alongside oral pain medication and physical therapy.[163] They are often considered in patients with significant pain and functional limitation prior to shoulder replacement surgery.[164]

Efficacy of Acromioclavicular Joint Injections

To date, no RCTs have been published evaluating the long-term effectiveness of AC joint injections. A limited number of studies, including one RCT with a three-week follow up, reported short term improvement with IA injection in terms of AC joint pain.[165–167] A single prospective study involving 20 patients (25 shoulders) with primary AC joint arthritis with five-year follow up demonstrated significant, sustained pain improvement at 12 months that diminished by five years but was still improved compared to baseline.[168] AC joint injections may provide significant pain relief in patients with chronic AC joint pain who fail to respond to comprehensive conservative management, including pain medications, physical therapy, and activity modification.[169]

Hip

Anatomy

The hip joint is a ball and socket type of synovial joint situated deeply within the pelvis. Hip joint stability is attributed to the articulation of the convex femoral head (ball) into the concave acetabulum (socket), with additional reinforcement arising from the articular capsule and surrounding muscles and ligaments. The fibrous articular capsule extends from the acetabular rim across the joint to the base of the femoral neck.[170] This capsular anatomy allows for accurate IA injectate placement into the capsule at the femoral head/neck junction without going directly into the joint space. The femoral neurovascular bundle lies medially to the hip joint in the femoral triangle.

Indications and Musculoskeletal Pathology

Intraarticular injections may be used to diagnose and treat the symptoms of inflammatory and non-inflammatory arthritis of the hip joint. Osteoarthritis is a significant cause of hip pain and disability. Intraarticular hip injections are used as a non-operative treatment for hip osteoarthritis. Intraarticular hip injections are also utilized for diagnostic purposes to determine and distinguish IA hip pathology from extra-articular sources of pain.[171] Clinical predictors of a successful response include the presence of joint effusion[172] and lack of an atrophic radiologic pattern.[173] The radiographic severity of hip arthritis does not predict pain relief outcome for therapeutic IA hip injection.

Palpation Guided Anatomic Injection Technique

Multiple hip joint injection techniques are described in the literature, including palpation (anatomic landmarks) and image (fluoroscopy and ultrasound) guided techniques. Palpation guided injections include both anterior and lateral approaches. Intraarticular hip injections using anatomic landmarks are often inaccurate because of the joint's deep location.[174,175] Here, we will focus on descriptions of image guided techniques, which are associated with improved injection accuracy.[176–178]

Fluoroscopy Guided Intraarticular Hip Joint Injection Techniques

Anterior Approach

The patient is placed in the supine position on the fluoroscopy table. First, the femoral artery is identified with palpation along the inguinal crease.[179] With fluoroscopy under an anterior-posterior view, the lateral aspect of the femoral head/neck junction is identified.[149] A needle is then directed coaxially under fluoroscopic guidance to the lateral femoral head/neck junction while avoiding the previously marked femoral artery. After reaching the lateral aspect of the femoral head/neck junction, the needle is slightly withdrawn. Following negative aspiration, a radiographic contrast agent is injected to confirm the intracapsular needle placement. Corticosteroids, often with local anesthetics, are then injected (Table 67.2).

Lateral Approach

The patient is placed in the lateral decubitus position on the fluoroscopy table with the targeted hip in the non-dependent position. The skin entry point is identified immediately proximal to the greater trochanter. The center of the hip joint often corresponds to the midplane between the anterior and posterior aspects of the thigh.[180] In the anterior-posterior view, the needle is advanced to the lateral aspect of the femoral head/neck junction (Fig. 67.5). Care is taken to avoid an anterior or posterior needle trajectory to

• **Figure 67.5** Fluoroscopy guided lateral approach hip joint injection. An anteroposterior fluoroscopy guided view is used to position the needle for a lateral approach hip joint injection. The needle tip is positioned at the lateral femoral head/neck junction. Injection of radiographic contrast medium confirms accurate intracapsular needle placement. The *arrows* point to the needle. *Asterisk (*)* outlines the intracapsular radiographic contrast agent spread. (Please see text for a detailed description of patient positioning.)

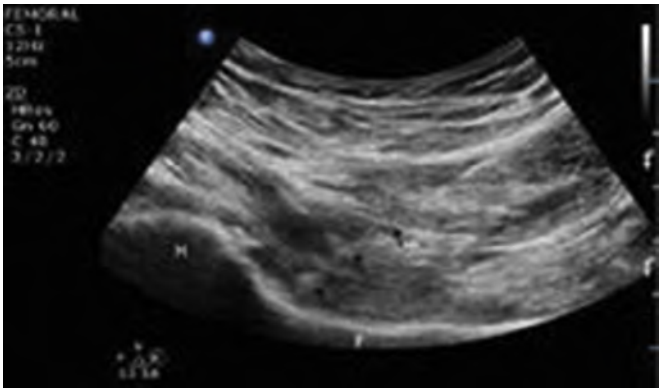
the femoral head/neck junction. On the fluoroscopy image, if the needle has passed the femoral head/neck junction without contacting bone, the needle must be repositioned to ensure intracapsular injection. Corticosteroids are then administered, often with local anesthetics (Table 67.2). Proposed advantages of the lateral approach include a skin entry distant from the femoral neurovascular bundle and visualization of the needle throughout placement.[179]

Ultrasound Guided Intra-articular Hip Injection Techniques

The patient is placed in the supine position on the procedure table. Typically, a low frequency curvilinear probe is employed to allow for adequate penetration and a larger field of view.[181] The femoral neurovascular bundle is identified in the short axis view. Then, the probe is moved laterally and oriented to align it parallel to the long axis of the femoral neck. In the anterior-oblique-sagittal (anterior-longitudinal) view, the femoral neck, femoral head, acetabular rim, and anterior synovial recess should be visualized.[178,181,182] The anterior synovial recess at the femoral head/neck junction is the target location. In this view, the femoral neurovascular bundle is located 20–30 mm medial to the desired needle trajectory.[182] Power or color Doppler is utilized to identify any overlying vascular structures such as the ascending branch of the lateral femoral circumflex artery.[183] The ultrasound view is adjusted to provide a needle trajectory that is clear of any vascular structures. A 22-gauge needle is advanced with an in-plane approach into the anterior synovial recess (Fig. 67.6). After confirming the needle position within the synovial recess, the medication is injected slowly while noting the expansion of the anterior hip capsule.

Efficacy of Intra-articular Hip Injections

Limited data exist that evaluate the efficacy of IA hip injections for osteoarthritis. Efficacy data for IA knee injections cannot be extrapolated to the IA hip injections because of differences in anatomical and functional characteristics. Three prospective randomized controlled studies suggest short-term efficacy for pain relief and functional outcome with visually guided (ultrasound or fluoroscopy) administration of corticosteroids.[172,184,185]



• **Figure 67.6** Ultrasound guided intraarticular hip injection. The *arrows* indicate the needle tip accurately placed within the synovial recess at the femoral head/neck junction. *F,* Femoral shaft; *H,* femoral head. (Please see text for a detailed description of patient and ultrasound probe positioning.)

Accuracy and Efficacy for Injection Technique Comparisons

Although multiple studies have recommended image guidance to improve accuracy, no studies have directly compared image guided versus palpation guided techniques.[173,174,176–178] Conventional palpation guided IA injections may result in inaccurate needle placement. The femoral neurovascular bundle is the primary anatomic structure at risk of injury.[174,186] Accuracy rates of 60%–80% for IA injectate placement have been documented with palpation guided techniques.[174–176,187]

Ultrasound guided IA hip injections have demonstrated accuracy rates of 97%–100%, which are comparable to the accuracy rates associated with CT or fluoroscopy guided injections.[178,187] Given the paucity of clinical outcome studies, no conclusive relationship can be established between improved accuracy rates and clinical and functional outcomes. Further evaluation is warranted regarding the safety and efficacy of IA hip injections, with direct comparison necessary between fluoroscopy and ultrasound guided techniques.

Knee

Anatomy

The knee joint is a synovial joint composed of three bones: the patella, femur, and tibia. The four major ligaments providing stability to the knee are the anterior cruciate, posterior cruciate, medial collateral, and lateral collateral.[188,189]

The medial and lateral menisci are fibrocartilaginous structures that provide stability, lubrication, and nutrition to the joint space. Meniscal tears occur three times more frequently in the medial meniscus. Knee flexion and extension are the main motion planes. The knee is divided into three major compartments: medial, lateral, and patellofemoral. Knee arthritis typically occurs in two or more compartments.[189,190]

The articular (sensory) branches innervating the anterior knee joint capsule are the targets of radiofrequency ablation lesions. A recent detailed cadaveric study described the highly variant anatomy of the genicular nerve branches that are targeted by needle placement under fluoroscopic guidance at key bony anatomic landmarks.[191] The superolateral quadrant is innervated by the nerve to the vastus lateralis, nerve to the vastus intermedius, the superior lateral genicular, and common fibular nerves. The inferolateral quadrant is innervated by the inferior lateral genicular and recurrent fibular nerves. The superomedial quadrant is innervated by the nerve to the vastus medialis, nerve to the vastus intermedius, and superior medial genicular nerve. The inferomedial quadrant is innervated by the infrapatellar branch of the saphenous nerve. The inferolateral quadrant is not a lesion target because of the location of the common peroneal nerve and one of its divisions (i.e. recurrent fibular nerve), the coagulation of which result in motor nerve injury.

Indications and Musculoskeletal Pathology

IA knee injections with either corticosteroids or viscosupplements are part of the non-operative management of knee osteoarthritis. In 1997 viscosupplementation was approved in the United States to treat knee osteoarthritis. For knee osteoarthritis, patients with evidence of severe damage or degeneration on x-ray or MRI may be less likely to respond to IA injection with corticosteroid than

those with mild structural damage.[192] Other factors negatively associated with the likelihood of improvement in pain and function to IA knee injection include more restricted range of motion, local knee tenderness, and older age.[193,194–197]

Injection Techniques

Palpation Guided Anatomic Knee Injection Techniques

Commonly utilized knee portals for IA injections include superior anteromedial, superior anterolateral, inferior anteromedial, inferior anterolateral, and lateral and medial midpatellar approaches. Multiple studies have examined different injection techniques in specific populations. In individuals without knee effusions, confirmation of appropriate needle placement can be difficult when using a palpation guided technique. Jackson et al.[198] demonstrated that the lateral midpatellar approach resulted in a higher accuracy rate (93%) in comparison with both the anteromedial (75% accuracy) and anterolateral (71% accuracy) approaches. The anteromedial and anterolateral injections were performed inferior to the patella, with the affected leg over the side of the examination table and the knee flexed to approximately 90°.

A cadaveric study compared four different IA injection sites (anteromedial, anterolateral, lateral midpatellar, and medial midpatellar).[199] The midpatellar approaches were performed with the knee extended on an examination table. The anteromedial and anterolateral injections were performed inferior to the patella with the leg over the side of the examination table and the knee flexed to approximately 90°. The accuracy rate was highest for the anterolateral approach (85%) and lowest for the medial midpatellar approach (56%).

Wind and Smolinski[200] examined injection portals superior to the patella (superolateral and superomedial) for low-volume (2–3 mL) injections, consistent with viscosupplementation treatment. Injections were performed with the knee extended. In this study, the lateral joint line injection was unreliable and resulted in IA placement less than 50% of the time.

Fluoroscopy Guided Knee Injection Techniques

Techniques have been described for fluoroscopic needle advancement, and fluoroscopic confirmation of appropriate injectate location following palpation guided IA injection.[149,201] The fluoroscopy guided injection technique can be performed above (Fig. 67.7), below, or at the level of the patella. When the injection is performed at the patellofemoral joint with either a medial or lateral approach, the patella is manually displaced away from the needle, and the needle is advanced into the joint.[149] In individuals with severe patellofemoral joint arthritis, access into the joint may be difficult with this technique.

Anterior approaches have also been described.[202,203] Moser et al.[203] assessed the infrapatellar anterolateral and anterior paramedian needle insertion approaches for technical success and patient tolerance levels during knee arthrography. For the anterior paramedian approach, the knee is flexed to 60°, and the needle is introduced just lateral to the inferior patellar ligament and directed cephalad and medial toward the femoral notch. For the anterolateral approach, the knee is flexed to 90°, and the joint space is located. The needle is placed at the joint line and directed posteriorly and slightly medial toward the lateral femoral articular condyle.

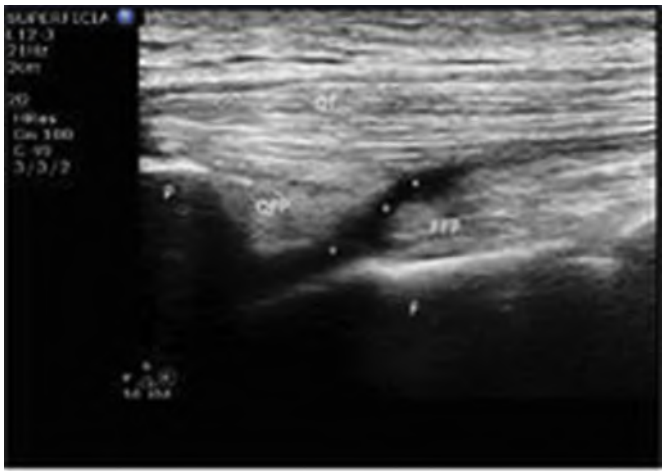
For the fluoroscopy guided techniques, radiographic contrast agent may be injected to confirm appropriate needle placement. If radiographic contrast cannot be utilized, IA placement has also been verified by mini-air arthrography.[201] For the superior patellar approach, mini-air arthrography can confirm IA placement when a sharply defined shadow of air is found in the suprapatellar pouch after 0.5–5 mL of air is injected.[201,204] Extra-articular placement is suggested when the air is found diffusely in the surrounding tissues. Although air arthrography has been suggested as a safe procedure, the Doppler function for ultrasound or a negative aspiration for fluoroscopy guided injections should be utilized prior to injecting air to prevent an intravascular injection and the possible development of an air embolism.

• **Figure 67.7** Fluoroscopy guided lateral approach for suprapatellar intraarticular knee injection. Accurate needle tip placement in the suprapatellar synovial recess is confirmed by appropriate localization of injected radiographic contrast medium. (Please see text for a detailed description of patient positioning.)

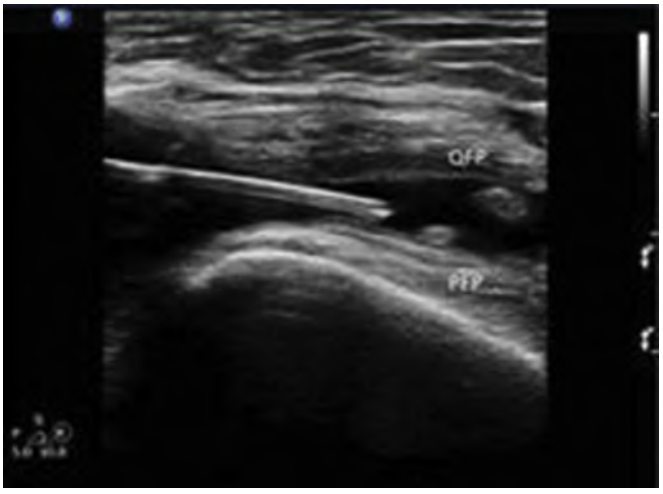
Ultrasound Guided Injection Techniques

Ultrasound guided approaches include the midpatellar lateral,[204] the midpatellar medial,[205] and the suprapatellar synovial recess[206] approaches. With both the medial and lateral midpatellar approaches, the patella prevents direct visualization of the needle and injectate in the IA space. Therefore the preferred technique is the suprapatellar synovial recess approach. This approach also minimizes the risk to soft tissue structures and the articular cartilage.[206] One disadvantage of this approach is that the suprapatellar synovial recess can be difficult to visualize in individuals without knee effusions.

For the suprapatellar approach, the patient is in the sitting or supine position with the knee flexed approximately 20–30°.[207] The knee should be supported with a pillow or rolled towel to allow relaxation of the quadriceps tendon. A high frequency linear-array probe is utilized. First, the knee is scanned with the transducer parallel to the longitudinal axis of the quadriceps tendon (Fig. 67.8). Then the skin and subcutaneous tissues, quadriceps tendon, patella, quadriceps fat pad, prefemoral fat pad, femur, and suprapatellar synovial recess are identified. The suprapatellar synovial recess is located between the prefemoral and quadriceps fat pads, and it communicates directly



• **Figure 67.8** Long axis view of the suprapatellar synovial recess. *P* indicates patella; *F,* femur; *PFP*, prefemoral fat pad; *QFP*, quadriceps fat pad; *QT,* quadriceps tendon. *Asterisk (*)* indicates the outline of the suprapatellar synovial recess communicating with the intra-articular joint space. (Please see text for a detailed description of patient and ultrasound probe positioning.)



• **Figure 67.9** Short axis (transverse) view of the suprapatellar synovial recess. The needle was accurately placed in the suprapatellar synovial recess between the prefemoral fat pad *(PFP)* and quadriceps fat pad *(QFP)*. (Please see text for a detailed description of patient and ultrasound probe positioning.)

with the knee joint. Transducer pressure must be minimized to prevent compression of the synovial recess. In some individuals, a significant effusion will be visualized in the synovial recess. Next, the transducer is rotated 90° to the axial (transverse) plane for the short axis view (Fig. 67.9), and the same structures are identified. The needle is advanced in the short axis view with an in-plane technique from lateral to medial into the suprapatellar synovial recess. Synovial fluid should be aspirated if there is a significant effusion. Then the injectate is placed into the joint under direct ultrasound visualization. The Doppler function can also be utilized to enhance the visualization of the injected fluid.

The suprapatellar synovial recess injection may also be performed with the ultrasound transducer along the longitudinal axis.[206] With this technique, the superior margin of the patella is the inferior landmark of the suprapatellar synovial recess. The transducer is moved laterally to avoid insertion into the quadriceps tendon. The cephalad end of the transducer is positioned more laterally than the caudal end. The needle is advanced in-plane in the long axis. This approach may be advantageous when it is difficult to view the suprapatellar synovial recess in the short axis (transverse) plane.

In a direct comparison of visually guided techniques to palpation guided techniques for knee IA injections, numerous studies have demonstrated greater accuracy with image guided methods.[110,205–208] For the suprapatellar approach, ultrasound guided IA injection resulted in greater accuracy rates (96%–100%) than palpation guided injections (55%–84% accuracy).[206,207] For the medial patellar portal, injection accuracy increased from 77% for blind injections to 96% for ultrasound guided injections.[205] Improvement in accuracy from ultrasound needle guidance positively and significantly influences clinical outcomes and cost effectiveness.[110,208] Improvement in outcomes using ultrasound guidance for arthrocentesis of the effusive knee included a 48% reduction in procedural pain and a 183% increase in aspirated synovial fluid volumes.[209] Short-term pain outcomes were also improved at two weeks post-injection. Although fluoroscopic guidance assists with needle placement, data have not yet been presented that demonstrates improvements in clinical or functional outcomes.

Efficacy and Safety of Intra-articular Knee Injections

A systematic review of 28 trials included comparisons of corticosteroids to placebo, viscosupplementation (hyaluronan and hylan derivatives), and joint lavage.[210] Injected corticosteroids were found to be superior to placebo in terms of pain relief at one week with a number-needed-to-treat of three. Increased pain reduction by injection versus placebo lasted up to three weeks. From four to 24 weeks, there was a lack of evidence to support prolonged therapeutic efficacy. Functional outcomes were difficult to evaluate, secondary to a lack of data. Corticosteroid injection and viscosupplementation benefits were similar between one and four weeks post-injection. From weeks five to 13, viscosupplementation was assessed as superior, with improvements maintained in functional and pain outcomes.

A systematic review of viscosupplementation for the treatment of osteoarthritis evaluated 76 trials.[102] Compared to a placebo, viscosupplementation was found to be superior. From five to 13 weeks post-injection, viscosupplementation improved pain relief from baseline by 28%–54% and enhanced function by 9%–32%. Although slower in onset, viscosupplementation appears to have a more prolonged therapeutic effect than IA corticosteroids.[211] Comparisons between different formulations of viscosupplementation could not be made secondary to differences in study designs and outcome measures.[102,194,212]

Radiofrequency Ablation

Conventional and internally cooled radiofrequency ablation (RFA) techniques induce a controlled, thermal coagulative necrosis at a specific lesion site using defined selected parameters, including tip size and time and temperature settings. These techniques are best described for the knee joint among large peripheral joints but are also employed for the hip and shoulder. RFA techniques have emerged as safe, effective, and economical alternatives to IA corticosteroid injections for painful osteoarthritis of the knee and are a viable option prior to joint replacement surgery in patients who are not surgical candidates.

Radiofrequency Ablation of the Knee Joint

Radiofrequency ablation of the genicular nerve involves thermal coagulation at three to four target areas, including the lateral superior, medial superior, and medial inferior genicular nerve branches and the middle branch from the vastus intermedius. Both fluoroscopy and ultrasound can be used to identify relevant landmarks needed to target these areas.[191,194,213] Prior to performing RFA, diagnostic blocks are often used to help identify patients that may improve with treatment. Although research is mixed regarding the prognostic capabilities of diagnostic genicular nerve blocks, further research is needed to determine the role of these injections. A recent prospective RCT evaluating the utility of genicular nerve blocks to predict the outcomes of genicular nerve RFA comparing the use of diagnostic blocks with a selection threshold of ≥50% pain relief to a no block group did not demonstrate increased treatment success using diagnostics blocks.[214] A recent multicenter RCT comparing the efficacy of internally cooled electrode radiofrequency ablation to IAS for knee pain because of OA found more favorable outcomes in terms of pain reduction, improved physical function, and reduction in nonopioid medication use in the RFA group.[196] In addition to possibly longer lasting therapeutic effect than IAS and sparing of steroid administration, RFA has the advantage of remaining a viable treatment option after joint replacement surgery, although robust evidence to support its use in the post-surgical population is lacking. A recent systematic review and meta-analysis of RFA of the genicular nerves for nonsurgical treatment of knee pain favored RFA treatment in all seven included RCTs, with no studies reporting serious adverse events related to the procedure.[215] RFA was shown to be superior to sham treatment, IA corticosteroid, and viscosupplementation among five high-quality RCTs and two moderate quality RCTs.

Although only three to four nerves are targeted in the traditional RFA technique, anatomic dissections demonstrate that over 10 nerves or branches provide innervation to the knee joint.[191] Future anatomic and clinical studies are needed to guide physicians in determining which nerves require lesioning for optimal clinical outcomes.

Fluoroscopy Guided Technique

The thermal radiofrequency ablation technique is the most common approach utilized. Three to four sites are the targets of the anesthetic blocks and cooled radiofrequency ablation lesions.[216] From an anterior-posterior (AP) view of the knee, these include periosteum at the junction of the shaft of the femur with the medial and lateral epicondyles (superomedial and superolateral genicular nerve branches) and the junction of the shaft of the tibia with the medial epicondyle (inferomedial genicular nerve branch), with the option of a fourth lesion target approximately 3 cm above the patella targeting the nerve from the vastus intermedius. The inferolateral genicular nerve branch is not targeted in order to avoid damage to the common peroneal nerve. The needles or introducer are advanced along the periosteum to 40%–60% the depth of the femur or the tibia in a lateral view for the genicular nerve branches, and the suprapatellar location is advanced to the periosteum, either through quadriceps tendon or using a lateral approach to pass underneath tendon and along periosteum. It is important to perform motor stimulation testing prior to proceeding with RFA for the ablation technique, stimulating each nerve branch at 2 Hz up to 2 volts and confirming no motor response. Each ablation site is then anesthetized for an appropriate period, and then ablation is performed.

Ultrasound Guided Technique

Genicular nerve block and RFA can be performed using ultrasound guidance, although this guidance modality is not demonstrated to be superior to fluoroscopic guidance in terms of safety or efficacy.[217] One advantage of using ultrasound guidance is the ability to directly visualize vascular structures in the vicinity of targeted nerves, avoiding the need to rely exclusively on periosteal landmarks for approximate locations of the nerves. The efficiency of the ultrasound guided technique is highly operator dependent.

Safety and Effectiveness of Radiofrequency Ablation of the Knee Joint

Genicular nerve RFA has been found to be generally safe and efficacious for at least three months.[212] However, case reports exist demonstrating injuries to vascular structures that can lead to the creation of abnormal vascular structures, hemarthrosis, and osteonecrosis.[194] Thirty-three studies including 13 RCTs examining the effectiveness and safety of RFA found that knee ablation techniques improved pain and function in subjects with knee pain because of osteoarthritis through follow up ranging from three to 12 months.[218] Thirteen of the studies examined pulsed radiofrequency using various parameters with respect to voltage (40–50 V), frequency (2–5 Hz), temperature (38.9°C–42°C), pulse width (5–20 ms) and duration (4–15 minutes). Five studies examined RFA with internally cooled electrodes, and 16 studies investigated conventional RFA using varied parameters in terms of temperature (60°C–80°C) and duration (60–120 seconds). Twenty-nine of the 33 studies reported adverse events (AEs), with nine of those studies reporting minor AEs including knee swelling, temporary periosteal pain during the procedure with cannula placement, hemarthrosis, subcutaneous bleeding at the needle insertion site, and hypoesthesia. There were no serious procedure related AEs reported, including infection, hemorrhage, motor damage, or thermal injury.

Although rare, the most concerning theoretical adverse effects of RFA of the knee joint include vascular injury, motor injury, and thermal injury to the skin. Arteries lying in close proximity to genicular nerve targets are at risk for injury from radiofrequency ablation of the genicular nerves, and although vascular injuries as a consequence of RFA are rare,[219] they are well described in the surgical literature.[194] Particular attention should be paid to the inferomedial genicular nerve branch target site, which involves a thinner dermal layer in many patients, and with which thermal injury to the skin has been reported using the conventional RFA technique.[220]

Genicular nerve RFA or RFA of the knee joint is an attractive alternative to traditional knee IA injection for several reasons, including sparing patients corticosteroid exposure and potentially longer lasting benefit following treatment. An RCT comparing cooled RFA to IA corticosteroid injection of the knee found superior results at six months in terms of 1) numeric rating scale (responders 50% or greater, 74.1%–16.2%, $P < 0.0001$), 2) improvements in the mean Oxford Knee Score (35.7 ± 8.8 to 22.4 ± 8.5, $P < 0.0001$), and 3) Global Perceived Effect (91.4%–23.9%, $P < 0.0001$).[196] There were no procedure related AEs. When selecting patients, an 80% or greater response to diagnostic anesthetic nerve blocks and duration of pain less than five years is associated with higher treatment success.[221] Radiofrequency ablation is also demonstrated to be a highly cost effective treatment for knee pain because of osteoarthritis.[222]

Radiofrequency Ablation of the Hip Joint

Although not as well described as RFA techniques targeting the genicular nerves, RFA may also be employed to relieve chronic hip pain because of osteoarthritis. The anterior hip capsule is the target

of RFA techniques of the hip joint, including a branch from the femoral nerve, the obturator nerve, and the accessory obturator nerve.[223]

Fluoroscopy Guided Technique

The patient is placed in a prone position and using either palpation or ultrasound guidance, the femoral artery is carefully marked with an indelible ink marker, taking care to be well lateral of this structure on needle entry. Moving from an AP pelvis view directly laterally, the femoroacetabular joint is visualized classically with the incisura in view. The articular branch of the femoral nerve is targeted at the 12 o'clock position on the superior acetabulum, with either the diagnostic nerve block needle or introducer needle against the periosteum at the lesion target site. For the articular branch of the obturator nerve, the needle is advanced typically from a position over the inferior ischium to advance the needle sagittal and deep to neurovascular structures to the bony ischium just lateral to the incisura. For the accessory branch of the obturator nerve, a second lesion is performed by advancing the needle approximately 1 cm cephalad. Care must be taken to advance along the periosteum without causing excessive pain, particularly as the introducer is advanced. Up to 1 cc of anesthetic is then injected for the diagnostic block. Motor stimulation is conducted prior to RFA lesioning.

Safety and Effectiveness of Radiofrequency Ablation of the Hip Joint

There is a far less robust body of literature including anatomic studies to guide clinicians in considering this option for chronic hip pain. However, a systematic review summarizing 14 studies investigating RFA procedures of the hip joint found a high success rate following treatment up to 36 months following the procedure. However, none of the studies were RCTs.[224] Similarly, there is little data to guide estimates of rates of AEs but reported AEs following hip RFA include hypoesthesia and hematoma, particularly at the target for the accessory obturator nerve, illustrating the importance of using caution and carefully identifying the femoral artery prior to needle entry.

Radiofrequency Ablation of the Shoulder Joint

RFA of the glenohumeral joint is a newer procedure relative to those targeting the knee and hip and the least well described in terms of safety and efficacy. Patient selection involves patients with intractable pain of the shoulder joint, acromioclavicular joint, rotator cuff, or adhesive capsulitis who are not candidates for surgery or who wish to employ conservative management for as long as possible. Nerve targets include the articular branches of the suprascapular nerve and axillary nerve posteriorly and the lateral pectoral nerve anteriorly.[225]

Fluoroscopy Guided Technique

The patient is placed in the prone position, and the arm is gently internally or externally rotated to optimally expose the greater tuberosity of the humeral head. For the articular branches of the suprascapular nerve, the C-arm is obliqued ipsilaterally, approximately 30–45° with a 15 degree caudal tilt. The articular branches of the suprascapular nerve targets lie on the posterior osseous rim of the glenoid fossa lateral to the spinoglenoid notch and inferior to the spine of the scapula. For the articular branches of the axillary nerve, the same fluoroscopic view was utilized. The posterior lateral humeral head and greater tubercle are located. The radiofrequency cannula is directed under fluoroscopic guidance to the posterior and inferior aspects of the greater tubercle just above the metaphyseal-diaphyseal junction. For the articular branches of the lateral pectoral nerve, the patient is repositioned to the supine position. For the lateral pectoral nerve, the C-arm is obliqued ipsilaterally, approximately 15° with a cranial tilt. The target is the center of the coracoid process.

Safety and Effectiveness of Radiofrequency Ablation of the Shoulder

There is a paucity of literature establishing knowledge with respect to the effectiveness and safety of the RFA technique for pain related to the shoulder joint, AC joint, and rotator cuff. A recent systematic review including 18 studies (six of which were RCTs) investigated the use of RFA for the management of chronic shoulder pain. Sixteen studies investigated pulsed RFA and two conventional RFA.[226] The study methodologies were so varied, including employing RFA techniques in combination with other treatments such as physical therapy or corticosteroid injection, and the RFA techniques themselves varied in terms of lesion parameters such that no definitive conclusions could be drawn regarding the efficacy of these techniques for the shoulder. Nevertheless, all studies reported positive results with RFA with few side effects, including several patients reporting transient tingling at the needle puncture site resolving within 1 hour and a single patient developing hematoma at the puncture site. The surgical literature describes thermal injuries to the skin occurring during arthroscopic acromioplasty,[227] and thermal injury should always be considered a risk with any percutaneous RFA procedure. Pulsed RFA targeting the axillary nerve[228] and suprascapular nerve[229,230] individually for shoulder pain syndromes is fairly well described, with poor quality of evidence supporting long-term efficacy but very reassuring safety profiles.

Conclusion

Joint injections are an important part of non-operative multimodal treatment for painful musculoskeletal conditions. Ultrasound and fluoroscopy guided IA injections assist in improving the accuracy of needle placement. Ultrasound is particularly helpful for interventional musculoskeletal procedures, offering advantages for specific procedures because of its ability to visualize periarticular soft tissues and provide real-time needle tracking without using ionizing radiation. The improvement in the accuracy of needle placement with ultrasound guidance for some joints is associated with significant clinical outcome benefits compared with palpation guided techniques. Future comparative studies are needed to develop guidelines for selecting the most appropriate IA corticosteroid and viscosupplementation agents and selecting the best methods to deliver these agents. Particular attention must be paid to the efficacy and adverse effects associated with the treatment of each joint and underlying musculoskeletal condition. Furthermore, optimal protocols for the timing of injection, post-procedure activity, and specific dosing regimens need to be defined. For some joint injections, larger scale studies are needed to directly compare the safety and efficacy of ultrasound guided IA techniques with traditional landmark-based and fluoroscopy guided techniques. As image guidance becomes more widely available and commonly utilized, palpation guided techniques for IA injections are used less and less.

Radiofrequency ablation is a newer therapy that is a safe and effective alternative to IA corticosteroid injections targeting knee, hip, and shoulder pain because of osteoarthritis. To date, the most comprehensive research exists for the knee joint. Additional research is needed to support the long term efficacy and safety of RFA for shoulder and hip pain.

Safe and effective performance of the procedures described in this chapter are critical to the development of an interventional practice, offering percutaneous therapies for the treatment of chronic peripheral joint pain because of osteoarthritis, including detailed knowledge of the relevant anatomy and potential risks to the patient from any procedure.

Key Points

- Musculoskeletal diseases, including symptomatic arthritis and soft tissue conditions, are associated with high levels of disability and significant economic costs. Osteoarthritis is the most prevalent form of arthritis.
- When joint injections are used, they should be incorporated into a multimodal treatment plan.
- Agents utilized for joint injections include corticosteroids, local anesthetics, and viscosupplements.
- Multiple corticosteroid and viscosupplementation formulations exist with differing pharmacologic properties.
- Viscosupplementation may have a more prolonged analgesic effect than IA corticosteroids but is no longer supported by the ACR guidelines for pain in joint arthritis.
- It is important to understand the adverse effects and complications associated with each injectate class. Appropriate management strategies should be employed when these events occur.
- Joint injections may be performed either with palpation, ultrasound guidance, or fluoroscopic guidance.
- Image guided techniques (ultrasound and fluoroscopy) have been shown to improve the accuracy of needle placement.
- Ultrasound offers advantages for specific procedures because it can visualize periarticular soft tissues and provide real-time needle tracking without ionizing radiation.
- Appropriate IA placement with ultrasound has been shown to positively influence clinical and economic outcomes.
- Radiofrequency ablation has emerged as a safe and effective alternative to corticosteroid injections for the management of chronic peripheral joint pain.
- RFA of the knee has the most robust evidence supporting its safety and effectiveness and may be considered in patients with or without prior knee surgery.
- RFA of the hip should involve a careful assessment of neurovascular structures, including consideration of using ultrasound guidance to identify the femoral artery.
- RFA of the shoulder is a newer technique with still evolving evidence regarding its safety and effectiveness.

Suggested Readings

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Myofascial Injections and Fascial Plane Blocks for Perioperative and Chronic Pain Management

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Overview and Pathophysiology of Myofascial Pain Syndromes

Myofascial pain is a common source of pain in the neck, low back, and other areas of the body. The term "myofascial pain" encompasses many different painful conditions, including muscle strain, myofascial trigger points (TrPs). It also includes specific myofascial pain syndromes, including piriformis syndrome, iliopsoas-related pain, and pain related to compression of the brachial plexus by the scalene muscles (neurogenic thoracic outlet syndrome). Skeletal muscle consists of muscle fibers under somatic nervous control. Each nerve root innervates a muscle or group of muscles known as a myotome. The muscle belly of skeletal muscles is connected by tendons to the bone. TrPs occur in the body of the muscle, most often located in the center of the muscle.

While much remains to be discovered about the pathophysiology of myofascial pain, several theories have been advanced in recent years. Underlying biomechanical and postural factors may interact with neurologic factors, psychological elements including depression and anxiety, and hormonal and nutritional imbalances. These factors (in total or in part) may create peripheral sensitization, autonomic dysregulation, and ultimately, central spinal cord sensitization, which can amplify the symptoms experienced by patients with myofascial pain. Vasoactive mediators, pro-nociceptive neurotransmitters, and inflammatory mediators including bradykinin, norepinephrine, serotonin, calcitonin gene-related peptide, substance P, tumor necrosis factor-α, and interleukin 1-B have been identified in the hypersensitive loci of TrPs.[1–3] These substances are pro-nociceptive and sensitize peripheral nociceptors. They are responsible for the sensory experience of myofascial pain, including referred pain and the local twitch response.

The motor phenomena seen in myofascial pain have been hypothesized to be caused by excessive acetylcholine (ACh) leakage, which creates dysfunctional endplates responsible for taut muscle band formation. Excessive ACh release leads to sustained muscle contraction by increased depolarization of the postjunctional endplate. Evidence of maximal sarcomere shortening in TrPs has been found in animal and human subjects.[4] A positive feedback cycle may be created by the interaction of increased ACh release, sarcomere shortening, and the release of sensitizing substances. The hypothalamus-pituitary-adrenocortical and sympathetic-adrenal-medullary system responses to experimentally induced stress in patients with myofascial pain revealed that plasma concentrations of cortisol, epinephrine, and norepinephrine were found to be significantly elevated in myofascial pain patients than in healthy controls.[5]

The taut muscle band present in myofascial pain syndrome has a higher resting tension and contains hypercontracted muscle fibers. Chronicity of this hypercontraction can increase local energy consumption and may cause areas of tissue hypoperfusion and ischemia. Vasoactive mediators are released in the setting of muscle ischemia, leading to increased ACh release, exacerbation of local ischemia, and sensitization of peripheral nociceptors, thereby causing pain. Vasoactive mediators such as those released in the taut bands of MP have been known to sensitize peripheral nociceptive nerve fibers such as those found in skeletal muscle. Nociceptors spontaneously discharge with a lower threshold to painful stimulation and exhibit discharge to non-painful stimuli in a sensitized state.[6] Over time, this heightened abnormal peripheral sensory input creates a state of central neuronal sensitization.[7]

The clinical manifestation of abnormal electrical activity in the TrP is called a local twitch response (LTR) and is believed to be mediated by a segmental spinal reflex.[8] LTR is elicited by deep palpation or needling of the TrP and leads to a brisk muscle contraction in the taut band. The location of the LTR is called the "sensory locus," which has been correlated histologically with sensory nerve receptors.[9] The "active locus" is the site where spontaneous electrical activity is recorded, the waveforms of which correspond to published reports of motor endplate noise. According to this model, the sensory locus and the active locus act as the nociceptor and the motor endplate and are distributed throughout muscle. Where these align and are highly concentrated, we observe myofascial TrPs. Abnormal spontaneous electrical activity is present at the site of TrPs, with excessive ACh release creating endplate noise seen on electrophysiologic studies at the neuromuscular junction.[10] Spontaneous electrical activity occurs in TrPs more frequently than in normal tissue and displays aberrant patterns in TrPs. Therefore this spontaneous electrical activity is distinct from normal endplate potentials. This abnormal electrical activity detected in TrPs is thought to be directly connected to excessive ACh release.

Clinical Presentation and Diagnosis of Myofascial Pain Syndromes

A careful history and physical exam remain the keystone of diagnosis. The most common presentation of myofascial pain syndrome includes the following diagnostic criteria: regional body pain and stiffness, limited range of motion of the affected muscle, twitch response produced from a taut band, referred pain from a TrP to a zone of reference, and resolution of the symptoms with local anesthesia applied to the TrP.[11] As discussed previously, TrPs are localized painful areas of skeletal muscle containing taut bands that can be exquisitely sensitive to digital pressure. TrPs may be active or latent. Active TrPs are present in patients with painful regional conditions. Latent TrPs are asymptomatic but may be revealed by deep palpation on physical examination. Latent TrPs have been found in the shoulder girdle muscles of 45%–55% of healthy young adults.[12] myofascial pain may occur after an injury, with chronic strain from repetitive microtrauma, or without any clear precipitating event. Aberrant body mechanics or postural abnormality may initiate or further maintain the problem. The quality of pain tends to be a deep "aching" of variable intensity, and the pain is confined to a specific anatomic region. Characteristic referred pain patterns are associated with specific muscles, although these referral patterns are often unreliable.[13] The muscles commonly involved are the trapezius, splenii, cervical and lumbar paraspinal, and quadratus lumborum.

It is essential to have hands on formal training in the physical examination of myofascial pain and TrPs to achieve a reliable result.[14] Musculoskeletal examination should be performed with the objective of identifying potential orthopedic or neurologic dysfunction that could have a role in generating secondary myofascial pain and dysfunction. Although there are no universally accepted diagnostic criteria for myofascial pain, physical findings may help establish a diagnosis. A distinct pattern of TrP findings may reveal itself in myofascial pain syndrome after a given insult.[15] These painful TrPs limit the full range of passive motion in the afflicted muscle group. While these findings have been suggested as diagnostic criteria,[16–18] investigators have found it problematic to demonstrate consistent agreement in the presence or absence of TrPs among examiners in blinded studies with control groups.[19–21] Discrepancies in diagnosis may be attributed in part to a lack of a standardized examination technique and variability in the interpretation of examination findings. Variations in muscle anatomy, physical conditioning, and deconditioning can pose obstacles to proper diagnosis as well. The most reproducible diagnostic findings on physical examination include identification of a TrP in an affected muscle, referral of pain to a zone of reference, and reproduction of the patient's regular pain on physical exam.

Differential diagnosis of myofascial pain should include (1) musculoskeletal and neuropathic disorders such as arthritis, degenerative disk disease, radiculopathy, bursitis, and tendonitis; (2) autoimmune or infectious etiologies; (3) metabolic and endocrine dysfunction including hypothyroidism; (4) psychiatric disorders including depression and anxiety; and (5) fibromyalgia or diffuse amplified musculoskeletal pain.

Imaging studies have only recently demonstrated anatomic changes associated with trigger points. Ultrasound examination combined with Doppler blood flow has been reported to allow visualization of trigger points, and ultrasound imaging can help direct muscle injection techniques (see later). Recently developed techniques using magnetic resonance and ultrasound elastography purport to reveal changes in intramuscular signal consistent with trigger points, but this technology has not yet been validated.[22,23]

Treatment of Trigger Points

Treatment of trigger points commonly includes physical therapy (manual release techniques, stretching and strengthening, conditioning, therapeutic modalities), trigger point injections (TPIs), dry needling and acupuncture, and transcutaneous electrical nerve stimulation.[24] A broad range of treatment modalities have been reported, but weak research methodology continues to limit interpretation of the results. Regarding medications, tizanidine, but not cyclobenzaprine, was noted to be efficacious for acute skeletal muscle spasms.[24] Diazepam, amitriptyline, and lidocaine patch were found to be effective, but literature support for the use of anti-convulsants in treating myofascial pain syndrome is limited. Although clonazepam appears to be effective, its use is limited by the side effects of depression, liver dysfunction, and difficulty weaning the patient from this drug. Nonsteroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen, appear to be effective when given with other agents, but not as monotherapy.[24]

TPI is a widely used invasive therapy wherein a needle is guided directly into a TrP that has been previously identified on physical examination. TPI is best utilized in a series of injections and as part of a comprehensive treatment plan that includes guided, structured physical therapy. This strategy can be particularly beneficial when TPI is initially employed to reduce pain in patients otherwise intolerant of physical therapy or stretching, allowing the physical modalities to be more effective.[25] The following conditions are contraindications to TPI: (1) infection, systemic or localized; (2) coagulopathy; (3) distorted or complicated anatomy; and (4) patient refusal.

Saline, corticosteroids, various local anesthetics including lidocaine and bupivacaine, botulinum toxin serotype A (BoNT-A), and dry needling have all been used and studied. Stimulation of the LTR in direct needling of the TrP is valuable in achieving immediate effect.[26] There is good evidence to suggest that there is no advantage of one injection therapy over another or of any drug injectate over dry needling.[27] In a systemic review of 23 RCTs, Cummings and White concluded that any effect derived from TPI is likely derived from the needle itself rather than any specific substance injected, as there was no difference in the therapeutic benefit of "wet" needling versus "dry" needling.[27] Their review also suggested that pain reduction with saline TPI is equal to pain reduction with local anesthetic TPI, both significant. Although adding corticosteroid preparation to local anesthetic is common, it has not been reliably shown to reduce pain more than TPI with local anesthetic alone. Despite the widespread practice of TPI for MP, there is no consensus regarding the number of injection points, frequency of administration, and volume or type of injectate. Controlled studies are needed to evaluate the comparative efficacy of TPIs and their potential benefits in long term pain reduction if any.

Botulinum toxin serotype A (BoNT-A) produces sustained and prolonged relaxation of muscles by inhibiting the release of ACh at the motor endplate and is itself an analgesic inhibiting central sensitization.[28] Commercially prepared BoNT-A is expensive and should be employed with care by a well-trained physician. Although this therapy is promising, the results of RCTs have been mixed, and multiple systematic reviews have concluded that the current clinical evidence to support the use of BoNT in the treatment of MPS is inconclusive. Ferrante et al. found no statistically significant improvement compared to placebo with BoNT-A injection when injected directly into painful TrPs for cervicothoracic MP.[29] They concluded that although it is intuitive for the clinician to consider therapeutic injection of BoNT-A as a treatment for MP

(given its *a priori* similarity to TPI), peculiarities inherent to the use of toxin instead of dry needling or local anesthetic must be accounted for (i.e. toxin spread through fascial planes), including the effects of dosing of toxin, volume of injectate, muscles chosen to inject, postural relations and abnormalities, and injection technique. Harden et al. were able to identify a short term (12-week) reduction in MP of chronic tension-type headache with BoNT-A injection compared to placebo.[30] Graboski et al. found no significant difference in BoNT-A versus 0.5% bupivacaine injected into TPs of patients with MPS, though both were effective in reducing pain below the baseline level.[31] Venancio et al. studied 45 MP patients assigned randomly to one of three groups: dry needling, 0.25% lidocaine TPI, and BoNT-A TPI, and assessed over a 12-week period.[32] While all three groups showed favorable response to treatment, the BoNT-A group demonstrated less use of rescue medication and less post-injection local sensitivity.[32] In another study, Nicol et al. reported that BoNT-A injected directly into painful muscle groups using a "follow the pain" and pattern injection technique instead of trigger points led to reduced average numerical pain scores, reduced number of headaches per week, and improvement in general activity and sleep quality of life measures.[33] Similar positive findings were seen in the studies by Benecke et al.[34] and Miller et al.,[35] wherein patients with cervical myofascial pain received BoNT-A using a fixed-location injection technique.

Trigger Point Injection Technique and Follow Up

After informed consent, the muscle is palpated, and the trigger points are identified and marked. The area is prepared in a sterile fashion, and a 25- to 27-gauge, 1.5 inch needle is inserted into the trigger point. A local twitch may be elicited at this time, or the patient verbally identifies the painful area. After negative aspiration, 0.25% bupivacaine, 0.2% ropivacaine, or 1% lidocaine is injected with or without steroid, either dexamethasone (4 mg in a 30 mL bottle of local anesthetic) or a low dose of particulate steroid (e.g. 20–40 mg of methylprednisolone or triamcinolone diluted in the local anesthetic solution).

Possible complications include bleeding, hematoma, nerve block, and infection. The patient should be monitored closely for bleeding, development of neurologic symptoms (numbness or weakness, urinary or bowel incontinence), or signs of infection. Depending on the location of the injection, the patient should be instructed on the signs and symptoms of pneumothorax (from neck, shoulder, thoracic, and anterior chest wall injections) or local nerve blockade (for example, inadvertent median nerve block with injection of the flexor carpi ulnaris).

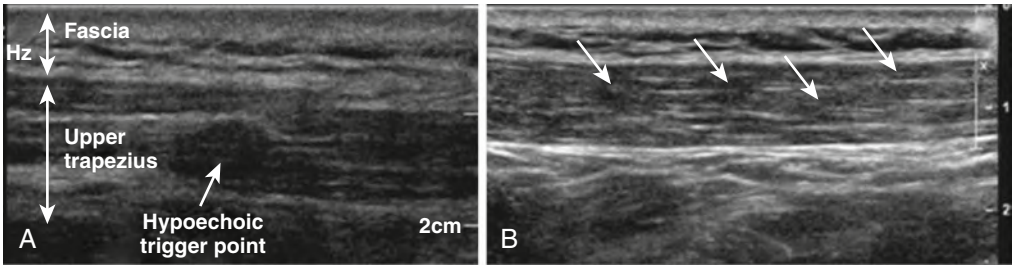
The success of the procedure is dependent on the diagnosis and localization of the trigger point. Patients with widespread chronic pain or psychological disorders are less likely to respond to TPI only. Patients with focal muscle pain and the characteristics of myofascial pain can achieve significant relief for days to months with a well-performed TPI. The success of TPI is often dependent on subsequent stretching and strengthening and neuromuscular education of the muscle.[1] The most effective treatment of myofascial pain syndrome is often a multi-disciplinary approach tailored to the individual needs of the patient that incorporates TPI with physical therapy and medication, as noted earlier. Practitioners are counseled to provide appropriate follow up after TPI and encourage patients to address other factors that perpetuate chronic pain (coping, employment, decreased social activity).[36,37]

Ultrasound Guided Trigger Point Injection Techniques

Ultrasound guidance provides several theoretical advantages over blind needle insertion. As stated, it allows visualization of the trigger point (Fig. 68.1). The practitioner is ensured that the needle is penetrating muscle tissue, which may be of use in patients with considerable adipose tissue, and can avoid local anatomic structures that are sensitive to needle penetration or local anesthetic infiltration (i.e. neurovascular structures or viscera).[38] Ultrasound imaging also allows visualization of the muscle twitch response with needle penetration, especially in muscles that are deep or small.[39] An additional use of the ultrasound is to confirm local anesthetic infiltration between fascial planes.[40] It also aids in blocking the spinal accessory nerve for diagnosis of trapezius muscle-related myofascial pain.[41]

Piriformis Injections

Piriformis syndrome is described in detail in Chapter 30 of this text but generally consists of pain in the buttock with or without radiation in the distribution of the ipsilateral sciatic nerve. It is considered the principal pain generator in approximately 8% of patients presenting with the buttock as the origin of pain. The syndrome can be a consequence of an abnormal relationship between the sciatic nerve and the piriformis muscle that results in irritation of the sciatic nerve. A hypertrophic muscle, infection, or invasion of the muscle by a tumor can cause pressure or irritation on the nerve.[42,43] In 78%–84% of the population, the sciatic nerve passes in front of the muscle. In 12%–21% of individuals, the divided nerve passes through or posterior to the piriformis and is exposed to muscle contractions, which trigger sciatic symptoms.[42] Piriformis syndrome is a diagnosis of exclusion since there are no

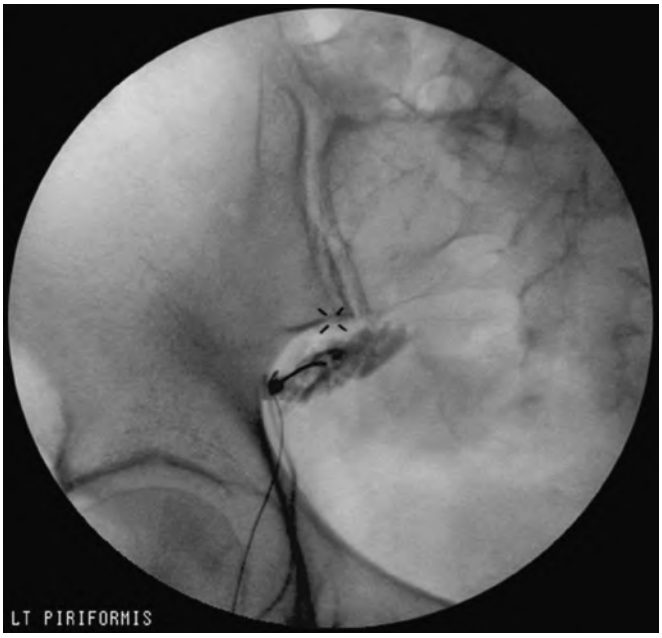


• **Figure 68.1** Gray-scale imaging of trigger points in the upper trapezius muscle. **A,** An isolated trigger point appears as a well-defined focal hypoechoic nodule. **B,** A series of four hypoechoic trigger points in the upper trapezius. (From Sikdar S, Shah JP, Gebreab T, et al. Novel applications of ultrasound technology to visualize and characterize myofascial trigger points and surrounding soft tissue. *Arch Phys Med Rehabil*. 2009;90:1829-1838, with permission.)

standardized diagnostic criteria for it. The syndrome should be considered in patients with buttock pain, tenderness to palpation over the piriformis muscle, and a positive response to provocative maneuvers, including:

1. Pace's sign: pain and weakness with seated abduction of the hip against resistance.
2. Lasègue's sign (also known as the straight-leg raise test): pain with unresisted flexion, adduction, and internal rotation of the flexed hip.
3. Freiberg's sign: pain with forced (i.e. against resistance) internal rotation of the extended hip.[42]

The piriformis muscle is usually injected under imaging guidance because of its small size compared to the gluteus muscles, its proximity to neurovascular structures, and its deep location. Studies have universally shown that the injections of local anesthetics and steroids can significantly reduce pain from piriformis syndrome, which holds true for the most common imaging techniques: fluoroscopic,[44,45] ultrasound guided,[46–48] and computed tomography (CT)-guided.[49] Other imaging guidance techniques include nerve stimulators and electromyography,[50] which were used more often prior to the increased availability of fluoroscopy and consistently improving the image quality of ultrasound.[51] Contraindications are the same as those noted in the section on TPI.[52]



• **Figure 68.2** Fluoroscopic image guided piriformis muscle injection.

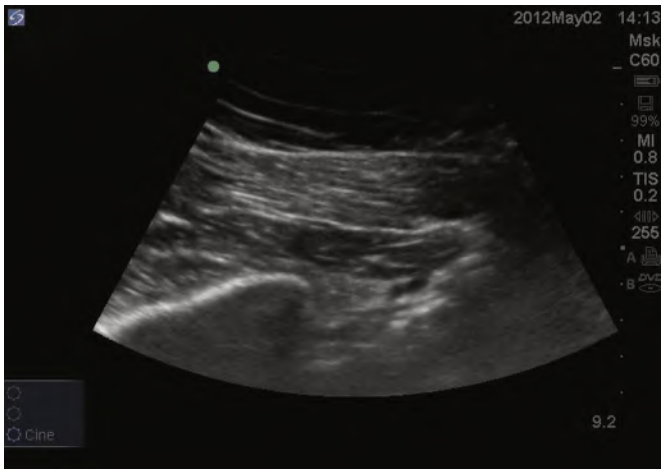
Combined Fluoroscopic Nerve Stimulator Guided Technique

The patient is placed prone on a fluoroscopy table, and the inferior margin of the sacroiliac joint is imaged and marked. The needle insertion site is 1–2 cm caudal and 1–2 cm lateral to the inferior margin of the sacroiliac joint. After sterile preparation and infiltration of local anesthetic, a 7–10 cm insulated needle is inserted and advanced with the nerve stimulator turned on (1 mA, 2 Hz, 0.1 ms) until an evoked motor response of the sciatic nerve is achieved (dorsiflexion, plantar flexion, eversion, inversion) at 0.4–0.6 mA. The needle is then withdrawn slightly until the sciatic stimulation disappears to avoid intraneural injection. Steroid (40 mg of either methylprednisolone or triamcinolone) plus 5 mL of saline is injected around the sciatic nerve—this is helpful, especially in patients with signs of sciatic nerve irritation. The needle is then pulled back 1 cm into the belly of the piriformis muscle, and 1–2 mL of contrast agent is injected. The contrast agent should outline the piriformis muscle belly with no sign of spillage (Fig. 68.2). After the characteristic spread of dye is achieved—outline of the piriformis muscle with clean margins—the local anesthetic solution with steroid is administered.

Ultrasound Guided Piriformis Muscle Injection Technique

The ultrasound guided technique permits a direct view of the piriformis muscle and allows examination of the anatomic variation in the relationship between the piriformis and the sciatic nerve. The patient is placed in the prone position with the ultrasound machine on the side opposite the operator. A curved, low-frequency ultrasound probe (2–6 MHz) is used to scan a wider and deeper area. The ultrasound machine should have Doppler to identify the inferior gluteal artery medial to the sciatic nerve and anterior to the piriformis. A 20- to 22-gauge, 10–12 cm long needle is recommended.

One technique involves positioning the transducer in the short axis (transverse) over the sacroiliac joint, where medially the sacrum will be visible, and laterally the ilium/gluteus maximus muscle complex will be observed.[47] While keeping the sacroiliac joint in the center of the screen, the transducer is moved caudally until the lateral view of the ilium is lost, which indicates that the transducer is over the greater sciatic notch. In this position, the operator will see the hyperechoic lateral portion of the sacrum medially. In the center of the image, the following are visualized: skin and fat in the near field and then the gluteus maximus muscle. Deeper to the gluteus maximus and originating from the anterior and lateral sacral edge is the piriformis muscle with its typical longitudinal fibers (Fig. 68.3). By moving the transducer slightly lower and mildly rotating the left gluteal area clockwise (counterclockwise on the right side), the sciatic nerve becomes visible deeper in the medial aspect of the piriformis. The ischium initially appears as a curved hyperechoic line (posterior acetabulum); more caudally, it becomes a flat line deeper to the piriformis. Another way to find the piriformis is to place the transducer over the line between the greater trochanter



• **Figure 68.3** Ultrasound anatomy of the piriformis muscle.

and ischial tuberosity. Once the sciatic nerve is identified, it is followed cephalad until the piriformis and gluteus maximus muscles are visualized overlying the sciatic nerve.

To confirm the view of the piriformis muscle, flex the patient's knee 90 degrees and rotate the hip internally and externally. During this maneuver, the piriformis will slide over the ischium while the position of the gluteus maximus remains stable. While observing the sciatic notch, it is useful to identify the ischial spine and differentiate other muscles close to the piriformis that insert in the area (i.e. the gemelli and obturator muscles).

The piriformis runs in a nearly axial plane between the sacrum and the femur. A lateral-to-medial, in-plane approach is ideal to maximize visualization of the needle; the needle enters the skin 3–4 cm lateral to the lateral edge of the transducer. The needle should cross the skin and fat in a lateral-to-medial, posterior-to-anterior direction and enter the gluteus maximus and then the piriformis in its medial half. Hydrodissection with normal saline (or a nonelectrolyte solution such as 5% dextrose if using stimulation) may help confirm the position of the tip of the needle before administering injectate. After injecting the piriformis muscle, to decrease sciatic nerve irritation, the needle can be advanced and positioned between the piriformis and the sciatic nerve to deposit injectate in that plane.

Injectate for Piriformis Target

Steroid

The most common combination for piriformis injectate is a corticosteroid (CS) plus local anesthetic (LA), often 5 mL of 0.25% bupivacaine plus 40 mg of methylprednisolone or triamcinolone. A retrospective study noted that 76% of patients treated with physical therapy and CS/LA injection had greater than 50% improvement at an average 10.5 month follow up.[53] A prospective study noted that patients had improved outcomes with CS/LA injection for a full year after treatment than with medication and physical therapy alone.[49]

Local Anesthetic

Although steroid injection is common, a 2015 randomized controlled trial (RCT) reported no difference in CS plus LA injection to the piriformis than LA alone. That said, both injection groups were clinically effective in treating pain.[54] It is not uncommon for weakness or numbness to develop in the distribution of the sciatic nerve for the expected duration of the LA.

Botulinum Toxin

Botulinum toxin is an increasingly common injection when the duration of effect from LA and CS injections is insufficient. A typical dose would be 100 mouse units in a 2 mL volume.[55] Due to its paralytic effect on the muscle, it causes atrophy and fatty degeneration of the muscle over time, as evidenced by magnetic resonance imaging (MRI).[56] This reduction in muscular volume would decrease pressure on the sciatic nerve and is the mechanism of analgesia,[51,53,57–63] but is a more profoundly effective treatment when combined with physical therapy.[53,58,61] Several uncontrolled studies have evaluated the use of botulinum toxin, often in combination with physical therapy, and reported high rates of success that lasted for months (Table 68.1).[55,57–62,64–67] A controlled study demonstrated the superiority of botulinum toxin over placebo injection for ten weeks.[60] Other controlled studies have reported that the efficacy of botulinum toxin is superior to that of local anesthetic/steroid or normal saline injections for the treatment of piriformis syndrome.[46,61,68]

Clonidine

When comparing clonidine versus normal saline as an additive to bupivacaine, a prospective study found a significantly lower pain score at six months in the clonidine group.[69]

Results of Treatment

Injection of the piriformis may improve pain related outcomes for several months. However, the published studies are limited by poor study methodology and reporting, inconsistent outcome selection, small sample sizes, heterogeneous patient populations, and the absence of standardized diagnostic criteria. The combination of a sciatic nerve conduction study with the flexion, abduction, internal rotation test may predict those who will respond to physical therapy.[53] More research into this topic comparing different treatment combinations would be welcome, but at present, it does appear that injection into the piriformis is an effective treatment modality for a patient that has failed conservative therapy.

Iliopsoas Injection

Pain emanating from the iliopsoas muscle is relatively uncommon but can be a source of inguinal, hip, or even low back pain. Patients typically have unilateral low back or anterior hip pain, although the pain can be referred to the thigh or inguinal area. Patients can vary widely, from young and active athletes, particularly those who participate in hockey, soccer, and dance, to older and more sedentary individuals who spend most of their time sitting, such as office workers and drivers. Myofascial pain arising from the iliopsoas muscle itself is distinct from that caused by iliopsoas bursitis or tendonitis (*coxa saltans* or "snapping hip syndrome"), although these causes are frequently included in the differential diagnosis. In addition, other causes such as lumbar spinal stenosis, iliotibial band syndrome, osteoarthritis or joint infection, inguinal hernia, and nerve entrapment syndromes should be considered.[70]

On physical examination, an antalgic gait because of a shortened stride on the affected side may be noted as the patient enters the examination room. The patient may also have pain or weakness when squatting to sit or when transitioning from a seated position to standing. The psoas muscle can be palpated deep in the abdomen, medial to the anterior superior iliac spine when the ipsilateral hip is flexed. Pain on palpation while flexing the hip against resistance is an excellent tool for diagnosing psoas major myopathy but may be uncomfortable for the patient. Provocative tests are not specific for the iliopsoas muscle but can aid in the diagnosis via active and passive extension of a painful muscle.[71]

- Thomas's test—The patient is supine and unable to extend the affected hip completely with the contralateral hip fully flexed; this is because of tightened hip flexors.
- Yeoman's test—The patient is prone and experiences pain with passive extension of the affected hip, typically a sacroiliac joint test but can cause anterior hip pain with passive iliopsoas extension.
- Gaenslen's test—The patient is supine and feels pain with extension of the affected hip (leg hanging off the examination table) while the contralateral hip is flexed (knee held to the chest), typically a sacroiliac joint test but can cause anterior hip pain with passive iliopsoas extension.
- FABER test—The patient is supine and experiences pain with *f*lexion, *ab*duction, and *e*xternal *r*otation of the affected hip.
- Snapping hip test—"Snapping" or "clicking" is heard when the hip is rotated from flexion and abduction to extension and adduction—this rules out *coxa saltans.*

TABLE 68.1 Results of Studies on Botulinum Toxin Injections for Piriformis, Iliopsoas, and Scalene Muscle Injections

Study	Muscle Injected	Type of Study	Groups Compared	Results
Porta[55]	Piriformis	Randomized, controlled	Botox A (100 units) vs. steroid	Pain scores were significantly lower in the Botox group 60 days after injection
Lang[57]	Piriformis	Open label	Botox B (5000 units)	Significant reduction in buttock and hip pain up to 16 weeks
Fishman et al.[61]	Piriformis	Prospective, dose ranging	Botox B (5000 7500, 10,000, 12,500 units)*	12,500 units superior to 10,000 units 12 weeks after injection
Yoon et al.[59]	Piriformis	Prospective, open label	Botox A (150 units) vs. lidocaine/dexamethasone (5 mg)	Improvement in SF-36 subscales (pain, physical and social functioning, vitality, general health) at four weeks
Childers et al.[60]	Piriformis	Double-blind, crossover	Botox A (100 units) vs. vehicle	Results better with Botox injection
Porta[55]	Iliopsoas	Randomized, controlled	Botox A (150 units) vs. steroid	Pain scores were significantly lower in the Botox group 60 days after injection
De Andrés et al.[64]	Iliopsoas	Randomized, controlled	Botox A (50 units) vs. 0.25% bupivacaine or NaCl (injected into the contralateral side)	No improvement with either treatment; no difference between groups; trend toward a decrease in pain scores with Botox
Jordan et al.[65]	Scalene	Prospective, open label	Botox (12–15 units per muscle)	64% of patients had >50% pain reduction for at least one month
Jordan et al.[66]	Scalene	Retrospective	Botox A (12–15 units per anterior/middle scalene); fluoroscopy/EMG guidance compared to ultrasound/EMG guidance	Results comparable: 91% good results with ultrasound and 81% with fluoroscopy
Christo et al.[67]	Scalene	Prospective	Botox (20 units) into the scalene muscle	Significant relief of pain for three months

Note: For botulinum toxin injection of myofascial trigger points, the preponderance of studies showed a lack of efficacy.

EMG, Electromyographic; *SF-36*, 36-Item Short-Form Medical Survey.

*The Botox injection was combined with physical therapy.

Relevant Anatomy

The psoas major muscle is located in the retroperitoneal space and consists of a deep layer that originates from the transverse processes of L1–5 and a superficial layer that originates from the lateral portions of T12–L4. The lumbar plexus is located between these two layers of muscle. The psoas major also has fibrous attachments to all the lumbar disks except L5–S1. According to their position, the attachments are categorized as either "anterior" or "posterior." The attachments located on the vertebral bodies and intervertebral disks are referred to as anterior fascicles, whereas those located on the transverse processes are known as the posterior fascicles.[72]

The psoas joins the iliacus muscle, which arises from the ilium, to form the iliopsoas muscle within the iliac fascia. This muscle then runs anterolaterally through the iliopubic (iliopectineal) eminence and the muscular lacuna beneath the inguinal ligament, next forms a tendon that sits anterior to the hip joint and finally inserts onto the lesser trochanter of the femur.[73] The psoas muscles are usually asymmetric in size, with the right side larger than the left. Innervation of the psoas muscle is achieved via the lumbar plexus from the ventral rami of L1–3, whereas the iliacus muscle is innervated by the femoral nerve from the ventral rami of L1–4.

Occasionally, a psoas minor muscle is present and arises from T12–L1. It follows the medial border of the psoas major and inserts into the iliopectineal eminence of the innominate bone and the iliac fascia at the pelvic brim. The psoas minor is absent in 40% of adults and can therefore be mistaken for lymphadenopathy on imaging studies. This muscle is considered a weak flexor of the spine and is innervated by the ventral rami of L1.[74]

Although it is widely accepted that the iliopsoas muscle aids in flexion and external rotation of the hip, there is controversy surrounding the muscle's other functions.[75] Other electromyographic studies have demonstrated varying degrees of activation of the iliopsoas muscle during hip rotation, adduction, and abduction, as well as during lumbar spine stabilization, flexion, and lateral flexion. As a result of these investigations, the iliopsoas muscle is thought to be "dynamically active" in that it adjusts its function according to spinal position and loading.[76]

To reduce friction between the bone and muscle, a large synovial-lined bursa with only a trace amount of fluid is located at the level of the iliopubic eminence. The bursa itself is relatively undetectable on many imaging modalities and requires MRI to

visualize it adequately. Additionally, the bursa communicates with the hip joint in a small percentage of adults, although the incidence rises dramatically in the setting of trauma or inflammation.[70]

Imaging

Iliopsoas syndrome can be confirmed via the history and physical examination alone, without the aid of special imaging. However, diagnostic imaging may be required because of the uncommon nature of the syndrome, and the diagnosis is frequently based on incidental findings. Multiple imaging modalities, including ultrasonography, CT, and MRI, can be useful in providing rapid and accurate information. CT can be used to outline the extent of affected tissue and may provide a diagnosis, such as infection or tumor. MRI can be used selectively in cases in which spinal canal or vertebral involvement is suspected.[74]

Ultrasonography has evolved to become a very useful modality for both the diagnosis and treatment of iliopsoas-associated disorders. Specifically, ultrasound can quickly identify abnormal motion of the tendon or assess for the presence of fluid in the muscle (e.g. abscess, hematoma). Other advantages to using ultrasound include the ability to scan the hip for assessment of symmetry and to direct injections into the muscle, tendon, or bursa.[77–79]

Technique

Basic Considerations

The same concerns that apply to any myofascial injection apply to iliopsoas injections as well. Care must be taken to ensure that the muscle is free of tumor, abscess, or hematoma before proceeding with an injection.

Fluoroscopic Technique

The patient lies prone with pillows placed beneath the abdomen to correct the lumbar lordosis. The L4 transverse process is visualized on anteroposterior fluoroscopy. After LA infiltration, a 3 inch, 22-gauge (spinal) needle is advanced until it touches the transverse process. For psoas muscle injection, the tip of the needle touches the superior aspect of the middle or the lateral third of the transverse process and is advanced 1 cm beyond the transverse process. Contrast agent is injected, and the muscle striation pattern is noted (Fig. 68.4). A lateral view is obtained and injectate administered. To inject the adjoining quadratus lumborum muscle, the needle touches the lateral tip of the transverse process and is advanced 1 cm. The same procedure as for the psoas muscle is then performed.

Ultrasound Guided Technique

Single-shot procedures, as well as catheter placement, can be accomplished safely with ultrasound guidance.[78,79] Two ultrasound guided techniques are described below.

Lateral Approach

The lateral approach is a technique modified from the one proposed by Kirchmair and colleagues.[80] This technique is recommended in patients with a body mass index lower than 35 since the ultrasound view will be impaired by a thick abdominal wall. The patient is placed in the lateral decubitus position with a mild anterior tilt. A low-frequency (2–6 MHz) curved probe is recommended. The transducer is initially placed lateral to the spine in a cross-sectional view, just above the iliac crest, to identify the transverse process and spinous process. The proceduralist then scans laterally around the waist of the patient with the probe perpendicular to the skin over the posterior axillary line, maintaining the transverse process in view. The following structures should be identified: skin, fat, lateral portion of the erector spinae muscle, quadratus lumborum, part of the external and internal oblique muscles, and the transverse process of L4. At this level, it is unlikely that the kidney will be in view unless the patient takes a very deep breath. The transducer is then moved laterally to obtain a full lateral view of the spine and paravertebral structures. The hyperechoic lateral portion of the vertebral body is seen as a thick line curving deeply in the anterior part; lateral to it is the cross-sectional cut of the psoas muscle between the lateral portion of the vertebral body and anterior to the transverse process (Fig. 68.5). Gentle, slow scanning of the psoas muscle while viewing the medial-posterior area will show the nerve root entering the muscle along with a segmental artery. In-plane needle access is recommended, with the entry point in the skin located about 4 cm medial to the medial/posterior end of the transducer. A 12–15 cm long, 20-gauge needle is used for single-shot injections, whereas a long epidural needle is required to insert a catheter into the muscle. The needle is advanced toward the junction between

• **Figure 68.4** Fluoroscopically guided iliopsoas muscle injection.

• **Figure 68.5** Ultrasound guided iliopsoas muscle injection.

the posterior and middle third of the muscle (in the anteroposterior plane) (see Fig. 68.5). If a catheter is planned, it should be advanced 2–3 cm beyond the tip of the needle under direct vision, with the bevel of the needle facing cephalad along the fibers of the muscle.

Posterior Approach

The patient is prone with a pillow under the abdomen to obtain a flat, more superficial spine position. In this approach, the same curved transducer probe is initially positioned longitudinally over the spinous process at the level of L3–4. The spinous processes are identified, and the transducer is moved laterally to show the laminae, masses of the facet joints, and finally, the transverse processes of L2–4, which appear like a trident on the ultrasound monitor.[81] Careful observation while the patient flexes the ipsilateral thigh against the table will demonstrate the fibers of the psoas muscle in between the transverse processes. The needle is oriented such that it crosses in between the transverse processes of L3 and L4 about 1.5 cm deeper than the distance measured from the probe to the posterior surface of the transverse process. When injecting in this location, no injectate should be observed superficially to the transverse processes. The catheter, if required, can be advanced similarly to the lateral ultrasound guided approach.

The patient should be monitored for signs of intravascular injection (the aorta or vena cava when the needle is too anterior), unilateral lower extremity weakness from lumbar plexus blockade, or bilateral lower extremity weakness as a result of epidural or subarachnoid injection (the needle is too medial or larger volumes are injected).

Results of Treatment

Stretching in combination with dry needling was reported to be very effective in a case series.[71] Standard physical therapy interventions such as stretching, strengthening, and improving neuromuscular control with the assistance of appropriate physical modalities (such as heat and therapeutic ultrasound) are also effective in the treatment of iliopsoas syndrome and associated musculotendinous disorders.[82]

Steroid and Local Anesthetic Injections

Iliopsoas injections are generally beneficial with judicious patient selection. A 2019 prospective study demonstrated that in patients with iliopsoas tendinopathy, the outcomes of injection were positive regardless of co-existing intra-articular hip abnormalities.[83] Similarly, if the iliopsoas tendon is painful, the patient will benefit from bursal injection even if the physical exam does not demonstrate snapping hip or tendinopathy.[84] A 2020 retrospective study showed that injection improved joint function and improved lower back and groin pain.[85] An example of typical injected medications would be 6–8 mL of LA (0.25% bupivacaine) and steroid (40 mg methylprednisolone or triamcinolone).

Botulinum Toxin Injection

One controlled study reported the superiority of botulinum toxin injection (150 units in a 3 mL volume) over steroid and LA.[46] This was similar to the 2000 study by Porta that showed benefit from botulinum toxin.[55] This is in contrast to another controlled study using a side to side comparison in the same individuals who did not benefit from botulinum toxin injection over LA or saline injection (Table 68.1).[64]

Truncal Blocks

Introduction

Surgeries of the thoracic wall are exceedingly common and are an underrecognized source of chronic postsurgical pain from incisional disruption of nerve fibers. Thorascopic or open thoracic surgeries are common culprits for postsurgical pain,[86] as are neoplastic or cosmetic breast surgeries.[87] In this section of the chapter, we will discuss the various regional techniques developed to provide postoperative analgesia for breast surgery but are now widely used to treat pain following thoracic surgeries or the acute pain of rib fractures. In contrast to peripheral nerve blocks, fascial plane blocks provide analgesia via the spread of LA along fascial planes or by diffusion through muscle tissue. Although the affected area is not as circumscribed or consistent as in neuraxial or targeted nerve block techniques, fascial plane blocks are particularly well-suited for providing analgesia to broad areas of the thorax.[86] By reducing the acute pain burden of surgical or traumatic insults, we reduce the likelihood of resultant chronic pain from these surgeries.[88]

Quadratus Lumborum Block

Quadratus lumborum block (QL) is not commonly a target for the treatment of chronic back pain but instead is an option for regional anesthetic management of the perioperative patient. It was first described in 2007,[89] and can be performed by one of three approaches. The QL has been shown to reduce pain in abdominal surgery,[90] renal surgeries,[91,92] laparoscopic hepatectomy,[93] and Cesarean delivery.[91,94–96] It has been shown to be superior to intravenous (IV) morphine for C-section,[97] and is comparable to epidural analgesia in laparoscopic nephrectomy.[98] Some RCTs have shown inferiority compared to spinal morphine,[99–101] and it does not necessarily provide superior analgesia to other regional techniques.[90,91,102] There are three approaches to the QL block, and the target of each varies.[103]

Lateral block (QL1): The needle is advanced to the transversus abdominis aponeurosis (between transversus abdominis and transversalis fascia), after which LA is injected at the lateral border of QL muscle. Injectate tends to spread to the transversus abdominis plane (TAP) and subcutaneous tissue anteriorly.[103]

Posterior QL block (QL2): LA is injected along the posterior surface of the QL muscle at the border between QL and erector spinae muscle. Injectate then spreads to the TAP and posteriorly along the middle thoracolumbar fascia intertransverse area.[103,104]

Anterior QL block (Transmuscular QLB or transverse oblique paramedian [TOP] QL3): LA is injected anterior to the QL muscle, in the tissue plane between the QL and psoas muscle. Injectate consistently spreads to the anterior aspect of the QL muscle and will occasionally spread interfascially to the lumbar nerve branches or thoracic paravertebral space.[104] Several approaches to this block variation have been described, including the transverse oblique approach and the paramedian sagittal oblique or subcostal approach.[103–106] This approach is not a one-size-fits-all technique, as an RCT showed that the transmuscular QL block did not reduce opioid consumption after laparoscopic hysterectomy.[107] However, this approach did improve analgesia after laparoscopic nephrectomy,[108] and provided comparable analgesia as combined ilioinguinal and iliohypogastric nerve block when used in the regional anesthetic management of inguinal herniorraphy.[109]

Pecs I Block

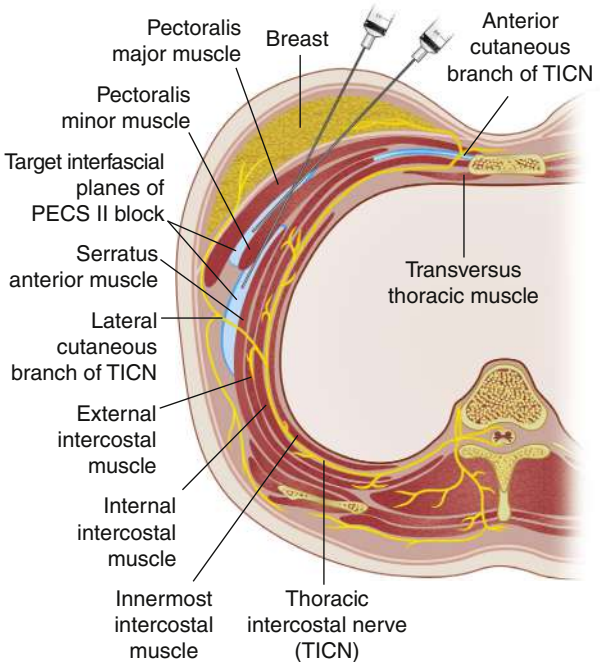
An ultrasound guided fascial plane block, the PEC I block, targets the medial and lateral pectoral nerves. These nerves lie in the fascial plane between the pectoralis major and minor muscles, and proper execution will anesthetize the pectoralis muscle (Fig. 68.6). The PECS I block as an isolated block has fallen out of favor, especially after a 2020 RCT demonstrated that it did not provide better pain relief than a placebo.[110]

Pec II Block

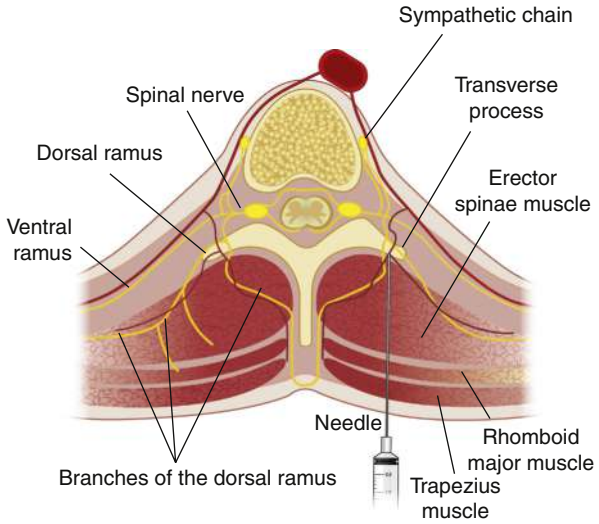
The Pecs II block includes the Pecs I block but adds another injection laterally at the fascial plane that separates the pectoralis minor and the serratus anterior (Fig. 68.6). This extension of block surface area targets the upper intercostal nerves. Compared to the PECS I block, the PECS II has been shown to provide markedly superior analgesia.[111–114] The PECS II also provides improved pain relief compared to paravertebral block in terms of reduced opioid use, reduced pain score,[115] and improved duration of analgesia.[116] Similarly, it is superior to erector spinae plane block in reducing pain scores and opioid use postoperatively,[117] which was also shown in a 2020 meta-analysis.[118] Lastly, if an interscalene targeted nerve block is added to the PEC II block, this combination is superior to interscalene block alone.[119]

Erector Spinae Plane Block

The group of muscles that comprises the spine-stabilizing erector spinae group are the longissimus, iliocostalis, and spinalis muscles. These originate from the spinous and transverse processes and extend laterally to insertion points that are variable based on the craniocaudal level of the spine (Fig. 68.7). Forero et al.[120]



• **Figure 68.6** Schematic of anatomic location of needle placement for PEC I and PEC II blocks. Kim D-H, Kim S, Kim CS, et al. Efficacy of pectoral nerve block type II for breast-conserving surgery and sentinel lymph node biopsy: a prospective randomized controlled study. *Pain Res Manage.* 2018:4315931.



• **Figure 68.7** Anatomic rendering of needle placement for erector spinae block. Shim J-G, Ryu K-H, Kim PO, et al. Evaluation of ultrasound-guided erector spinae plane block for postoperative management of video-assisted thoracoscopic surgery: a prospective, randomized, controlled clinical trial. *J Thor Dis.* 2020;12(8):4174–4182.

introduced the erector spinae plane block (ESPB) in 2016 as an attractive option for analgesia because although it is not as effective as epidural analgesia,[121] it is less invasive and does not require cessation of anticoagulation like the paravertebral block or neuraxial techniques. ESPB does not access the neuraxial space, but the precise nerve targets through which the LA generates analgesia are still a source of divisive discourse. Potential mechanisms include 1) LA spread via the fascial plane to the posterior rami of the spinal nerves,[122] or 2) anterior spread to the paravertebral space with spread to the sympathetic chain. Involvement of the sympathetic chain is controversial, with some cadaveric data showing dye spread superiorly, inferiorly, and laterally only with no spread anteriorly to the paravertebral space.[123] Another cadaveric study showed that 10 mL volume of injectate did not spread to the paravertebral space, while a 30 mL volume did spread minimally to this space on one occasion.[124] However, clinical reports suggest that ESPB anesthetizes sympathetic fibers.[125,126] Therefore the balance of data is still inconclusive.

Although the mechanism of action still eludes clinicians, ESPB has become popular and well-studied in terms of clinical effects. The ESPB has now been described for use at multiple levels up and down the cervical and thoracic spine,[127–132] and can provide analgesia for thyroid surgery,[133] video-assisted thorascopic surgery (VATS),[134] mastectomy,[118,135] total abdominal hysterectomy (TAH),[136] pediatric splenectomy,[137] rib fractures,[138,139] and for chronic thoracic pain.[140]

As mentioned above, ESPB is not considered superior to the Pec II block for breast surgery, but it provides similar analgesia and side effect profile to the serratus anterior plane block (SAPB)[141] and to the thoracic paravertebral block (TPVB).[118] It is also superior to tumescent local anesthesia that is occasionally used in breast reduction surgeries.[142] As for thoracic surgery, ESPB is more effective than SAPB in analgesia,[143,144] quality of recovery at 24 h, and morbidity scores.[144] It was also equivalent to TPVB after VATS surgery.[134]

These clinical trials stand in contrast to two recent volunteer studies showing that the sensory area covered by the ESPB is the posterior thorax only and would be unlikely to improve analgesia in thoracic surgeries.[122,145] Most cadaveric and volunteer studies support that ESPB analgesia is achieved via the dorsal branches of spinal nerves. However, clinical studies in surgical patients suggest the mechanism is spread to the paravertebral space and potentially the sympathetic chain. Given a recent meta-analysis showing that ESPB confers statistically significant but brief and clinically inconsequential relief to breast surgery patients, patient selection is paramount when opting for this procedure.[146]

Serratus Anterior Plane Block

The SAPB is a further modification of the Pecs I & II blocks that targets the lateral cutaneous branches of the intercostal nerves in the fascial plane between the serratus anterior and latissimus dorsi (Figs. 68.8–68.10).[147] This block significantly improves postoperative analgesia in mastectomy patients compared to Pecs II block,[148,149] and ESPB[141] in some studies. However, other studies showed that in mastectomy, the SAPB is similar in results to the ESPB,[141,150] but both increased time to first required dose of IV morphine postoperatively and decreased nausea and vomiting.[150] Lastly, the SAPB has been effectively used for post-thoracotomy pain[151] and rib fracture pain.[152]

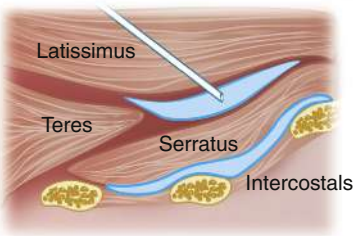
Scalene Muscle Injections for Neurogenic Thoracic Outlet Syndrome

Overview of Thoracic Outlet Syndrome

Thoracic outlet syndrome (TOS) remains a challenging, controversial, and frequently misdiagnosed neurovascular upper limb disorder.[153] TOS is a complex pathologic condition that presents with sensory and motor symptoms that may affect the neck, upper chest, shoulder, arm, and hand.[154] The incidence of TOS varies widely from three to 80 cases per 1000 people, and it exists in three different forms: neurogenic, venous, and arterial.[155] The most common type, neurogenic, accounts for 95% of all cases and is mostly seen in the third and fourth decades of life (Fig. 68.11).[155]

The thoracic inlet, also known as the superior thoracic outlet, refers to the opening at the top of the thoracic cavity. It is essentially a hole surrounded by a bony ring, through which several vital structures pass. TOS is caused by compression of the neurovascular structures passing through the superior thoracic outlet. It results from neck trauma (whiplash-induced injuries often from car accidents), repetitive stress injury, anatomic abnormalities (e.g. cervical ribs, elongated transverse process), muscle anomalies (presence of the scalene minimus muscle, sickle-shaped middle scalene), or a combination of these.[155] A small percentage of TOS cases are acquired through tumor metastases, osteomyelitis, or other uncommon sources.[156] Even though its cause is multifactorial, neurovascular compression at the interscalene triangle, costoclavicular, and retropectoralis minor spaces play an important role.[154] The cause of neurogenic TOS may be unknown in 12% of cases and related to a cervical or anomalous first rib in 2%. A cervical rib is an extra rib that arises from the seventh cervical vertebra. Their presence is a congenital abnormality. It is hypothesized that posttraumatic intrascalene muscle hemorrhage leads to scarring and spasm that cause pressure on the braquial plexus.[157]

Given that the estimated prevalence of the cervical rib in the general population is 0.5%–2%, and of neurogenic TOS is 1 per million; statistically, the presence of a cervical rib *per se* does not constitute a diagnosis for neurogenic TOS.[158] Cervical ribs occur in less than 1% of the general population.[158,159] Fifty percent are bilateral,[154] and 70% occur in females.[158] These have been reported in 5%–9% of patients with TOS.[159] Most cervical ribs are asymptomatic but can produce the neurogenic form of TOS more frequently than the vascular form.[155]



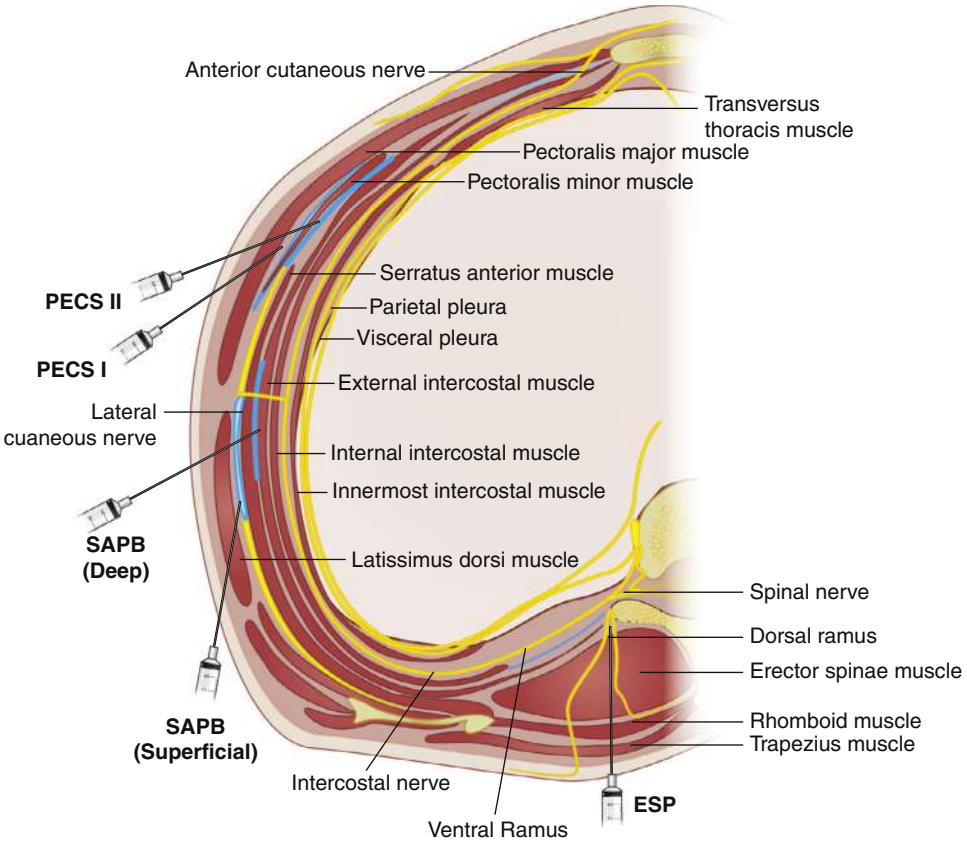
• **Figure 68.8** Anatomic location of the serratus anterior plane and needle placement for SAPB. Khalil AE, Abdallah NM, Bashandy GM, Kaddah TA. Ultrasound-guided serratus anterior plane block versus thoracic epidural analgesia for thoracotomy pain. *J Cardiothorac Vasc Anesth.* 2017;31(1):152-158.

Clinical Presentation and Diagnosis of TOS

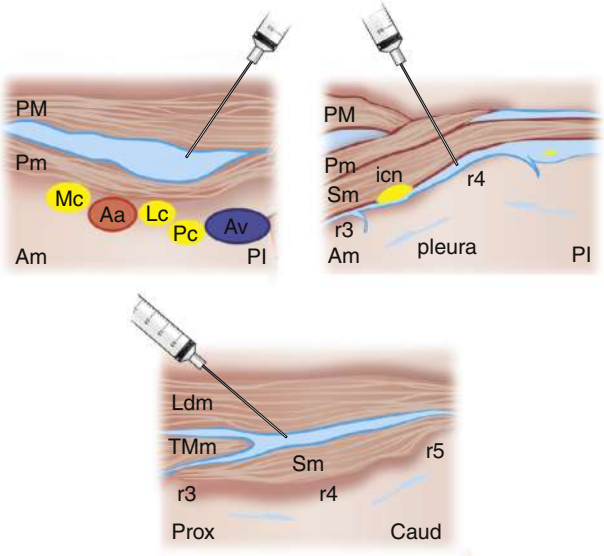
The diagnosis of neurogenic TOS (NTOS) is challenging since most patients present with subjective complaints of positional or exertional arm pain, fatigue, and paresthesia affecting the fourth and fifth finger predominantly.[157] Patients often have unilateral paresthesia, usually in the ulnar nerve distribution, weakness of the upper extremity, and variable other symptoms such as headache and cold intolerance. The diagnosis is difficult to make because of a lack of specific diagnostic criteria, the relative insensitivity of imaging modalities and other diagnostic testing, and a long list of differential diagnoses.[160]

Patients may present with symptoms of upper plexus compression (C5–C7), like pain on the ipsilateral aspect of the neck or mastoid area or even occipital headaches.[154,155] Symptoms are usually aggravated by continuous elevation of the arm.[155] Other symptoms are discoloration and cold intolerance of fingers in cases involving sympathetic fibers; and, less commonly, weakness of the upper extremity.[155] In patients with NTOS, clinical examination may reveal tenderness over the scalene and trapezius muscles, a positive Tinel sign over the brachial plexus, and a positive response to provocative maneuvers. Electromyography and nerve conduction velocity studies are helpful to exclude other causes of symptoms; however, this can be limited by low sensitivity in mild cases and false negative results.[157]

Paget-Schroetter syndrome, also referred to as "effort thrombosis," refers to primary thrombosis of the subclavian vein at the costoclavicular junction and is a form of venous TOS.[159] Clinical presentation is classic, with the patient complaining of a blue, swollen, heavy, painful arm. Patients typically present with sudden onset of an aching discomfort with a feeling of heaviness, swelling, and frequently a reddish-blue discoloration of the affected upper extremity.[159] Arterial TOS is associated with hand ischemia caused by either external compression of the subclavian artery or from emboli arising from a subclavian artery aneurysm. The symptoms of arterial TOS include digital ischemia, claudication, pallor, coldness, paresthesia, and pain in the hand but seldom in the shoulder or neck.[155]



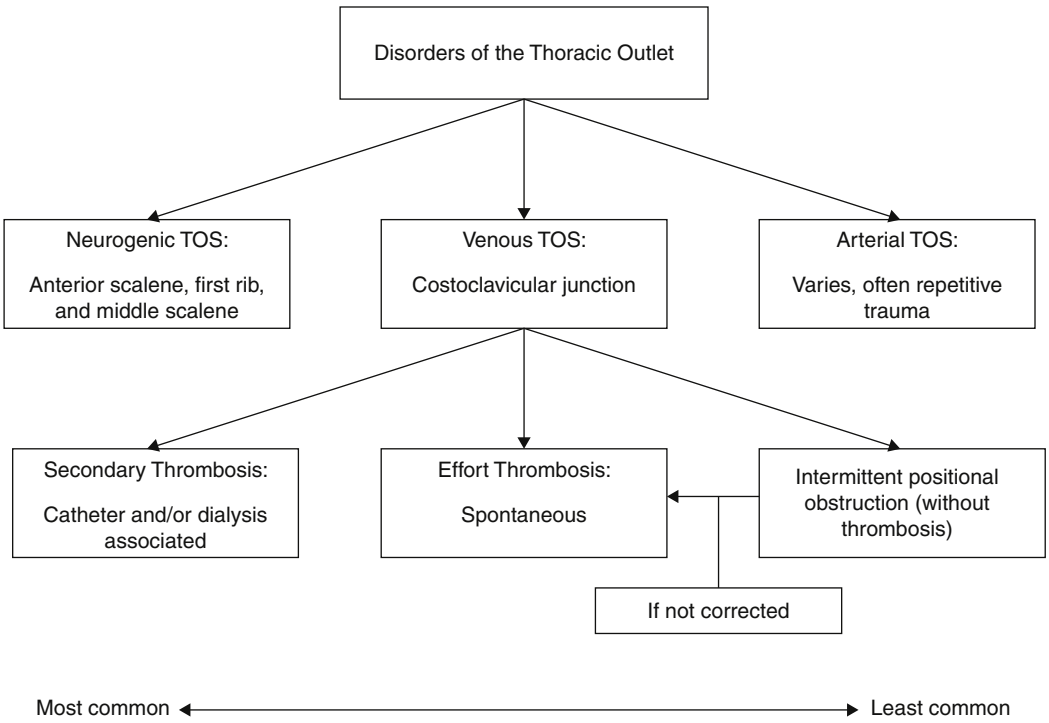
• **Figure 68.9** Anatomic comparisons of PECS I, II, erector spinae and serratus anterior plane blocks. Chin KJ, Pawa A, Forero M, Adhikary S. Ultrasound-guided fascial plane blocks of the thorax: pectoral I and II, serratus anterior plane, and erector spinae plane blocks. *Adv Anesth.* 2019;37:187-205.



• **Figure 68.10** Comparison of needle placement and plane location for PECS I & II and SAPB. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. *Anaesthesia.* 2013;68(11):1107–1113.

The treatment options for TOS may be conservative, such as stretching, massage, compression, injections on the scalene muscles with lidocaine, ropivacaine, bupivacaine, and botulinum toxin.[158] Despite being the main treatment option, surgical intervention for NTOS remains controversial.[154] Scalene muscle injections have been used to confirm the diagnosis of NTOS and predict the response of patients to surgery.[161] LA injections into the anterior scalene muscle alone or both the anterior and middle scalene muscles can relieve TOS. The injection relaxes the muscle or muscles elevating the first rib and mimics the effects of first rib resection or scalenectomy. Relief with this technique correlates well with successful physical therapy and surgical treatment.[157] Successful treatment of TOS with scalene muscle injection has been shown to be independent of any brachial plexus blockade.[162] However, to be predictive, the injection should avoid anesthesia of the brachial plexus and sympathetic chain, and the patient should be both medically and psychologically stable.[155] Different methods have been used to guide the scalene injection, including the use of anatomic landmarks, electromyography (EMG), ultrasonography, combinations of EMG and sonography, EMG and fluoroscopy, and most recently CT.[155]

Injections of medications such as local anesthetics or botulinum toxin (BTX) into muscles adjacent to brachial plexus, such as anterior scalene (AS) and pectoralis minor (PM), can help evaluate cases of suspected NTOS and provide temporary symptom relief.[154] Botulinum toxin type A (BTX-A) injection into the middle interscalene muscle or pectoralis muscle planes[153] is gaining popularity because it provides significant symptomatic relief and helps predict future surgical decompression success.[154] Recent evidence suggests anesthetic injections into the AS may predict surgical outcome in patients older than 40 years.[154]



• **Figure 68.11** Basic classification of thoracic outlet syndrome (TOS). Illig KA, Doyle AJ. A comprehensive review of paget-schroetter syndrome. *J Vasc Surg.* 2010;51(6):1538-1547.

Relevant Anatomy

The scalene musculature consists of three muscles located on the lateral aspect of the neck (Fig. 68.12). They have variable origin and insertion sites along the neck and frequently fused fascicles between the individual muscles. A fourth muscle is occasionally present, the scalene minimus. The AS arises from the anterior tubercles of the transverse processes of the C3–6 vertebral bodies and inserts onto the scalene tubercle of the first rib proximally and anterior to the subclavian artery. The middle scalene stems from the posterior tubercles of C2–7 and inserts onto the first rib posterolateral to the AS and posterior to the subclavian artery. The anterior and middle scalene muscles contain the brachial plexus between them. The posterior scalene originates from the posterior tubercles of C4–6 and inserts posterolateral to both the anterior and middle scalenes on the posterior border of the second rib. All the scalene muscles have multiple variations in their points of origin and insertion.[163]

The scalene muscles are cervical spine flexors. Cervical spine flexion results when the scalene muscles contract bilaterally, and lateral spine flexion results when the muscles contract unilaterally. Additionally, the scalenes serve as accessory muscles of respiration when the cervical spine is stabilized, with the anterior and middle scalenes helping to elevate the first rib and the posterior scalene elevating the second rib during deep inspiration. This group of muscles also rotates the spine ipsilaterally and reaches maximal stretch with contralateral rotation.[164,165] The scalene muscles are included in the posterior triangle of the neck, which is bordered by the trapezius posteriorly, the sternocleidomastoid anteriorly, and the clavicle inferiorly. Its apex is formed by the junction of the sternocleidomastoid and trapezius at the level of the occipital bone. Also within these demarcations are the brachial plexus (from roots to divisions), cervical sympathetic ganglia, spinal accessory nerve, phrenic nerve, subclavian artery, transverse cervical artery, and lymph nodes.

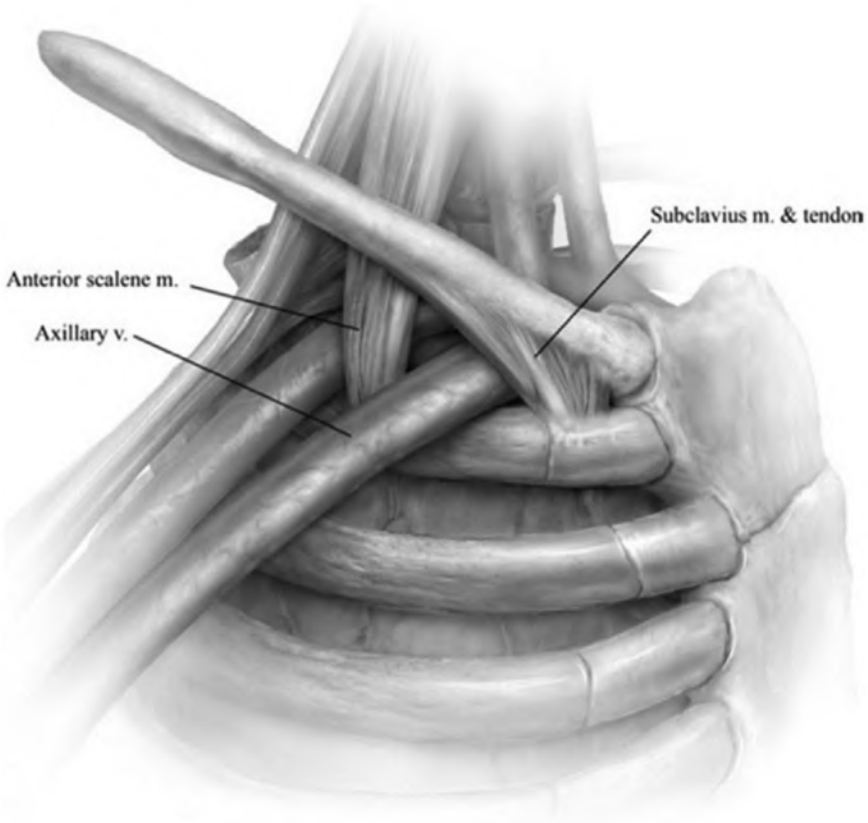
It should be noted that the interscalene groove, where the roots of the brachial plexus are located, is a potential groove. The anterior sheath of the interscalene groove is actually the posterior fascial sheath of the AS muscle, and the posterior sheath of the groove is the anterior fascial sheath of the middle scalene muscle.[162]

Imaging

Imaging modalities, including MRI, usually fail to reveal any abnormalities causing TOS. However, there are reasons to obtain imaging before performing any procedure in the posterior triangle of the neck. Such reasons include confirmation of muscle anomalies (presence of the scalene minimus muscle) and bone abnormalities (cervical rib, elongated transverse process), evaluation of the surrounding soft tissue for evidence of other injuries (e.g. rotator cuff tear), and identification of the presence of tumor, osteomyelitis, or other uncommon causes.

Injection Technique

Several techniques have been described to guide needle placement in the AS muscle, including the use of anatomic landmarks, and EMG alone or combined with ultrasonography, or image guided with ultrasonography, fluoroscopy,[157] or CT. With no imaging guidance, there is a high possibility of a false-positive result because of accidental brachial plexus anesthesia (10% of cases) or a false-negative result because of inaccurate targeting of the scalene muscles or inadvertent puncture of important vascular structures.[155] Contraindications to and concerns with scalene muscle injections are the same as those noted for trigger point



• **Figure 68.12** Basic anatomy of the thoracic outlet. Illig KA, Doyle AJ. A comprehensive review of paget-schroetter syndrome. *J Vasc Surg*. 2010;51(6):1538-1547.

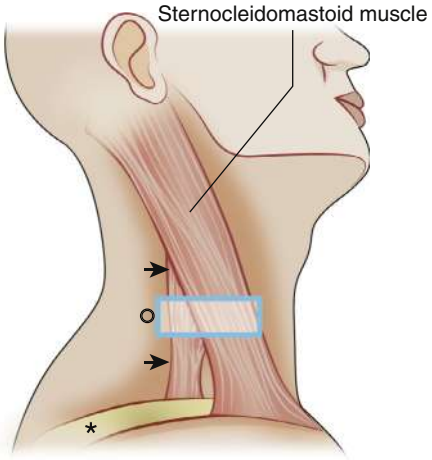
and piriformis injections. The ultrasound guided technique is preferred for safety reasons since the thyroid, esophagus, carotid, jugular vein, and brachial plexus are visualized, and hence this technique will be described.

Ultrasound Guided Technique

The patient is supine, and the area is prepared in a sterile fashion. Ultrasonography is used to visualize the anterior and middle scalene muscles through one of two approaches. The probe is placed at the level of the cricoid cartilage/C6 vertebra and moved laterally from the trachea, carotid artery, and internal jugular vein (compressible) to identify the two scalene muscles with the brachial plexus (hypoechoic nerve roots) between them. Alternatively, the ultrasound probe can be placed in the inferior (just above the clavicle) and lateral (lateral to the sternocleidomastoid) aspect of the neck. After identification of the subclavian artery and brachial plexus, the plexus is traced cephalad to the level of C7, in between the anterior and middle scalene muscles. After skin infiltration, a 1.5 cm, 21- or 22-gauge needle is advanced out of plane into the belly of the muscle away from the brachial plexus. The out of plane approach is preferable to avoid injection of LA into the brachial plexus.[162]

The AS muscle can be scanned along its craniocaudal extension and best visualized on images through its lower half. A lateral-to-medial needle approach is the preferred method to decrease the likelihood of vascular injury (Fig. 68.13).[157]

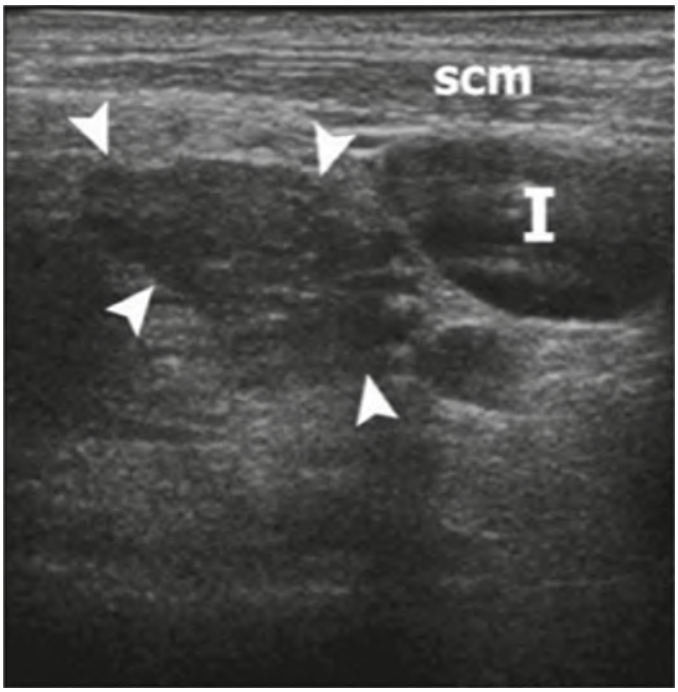
Approximately 1 mL of lidocaine 1% is injected subcutaneously at the previously marked site. A syringe containing 2 mL of bupivacaine 0.5% is connected to a 25-gauge 1.5 inch. Once



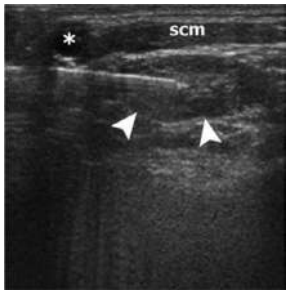
• **Figure 68.13** Approach for ultrasound guided injection of the anterior scalene muscle. Torriani M, Gupta R, Donahue DM. Sonographically guided anesthetic injection of anterior scalene muscle for investigation of neurogenic thoracic outlet syndrome. *Skelet Radiol*. 2009;38(11):1083–1087.

the needle tip is seen within the belly of the AS muscle, bupivacaine is slowly injected under real-time monitoring (Figs. 68.14 and 68.15).[157] Although some authors inject both the anterior and middle scalene muscles, others inject only the AS muscle.[162]

Relief of symptoms can occur within 15–30 min and may last for days or weeks. The brachial plexus may be blocked, with resultant numbness of the upper extremity, since it is not uncommon



• **Figure 68.14** Transverse ultrasound anatomy for anterior scalene muscle injection. Torriani M, Gupta R, Donahue DM. Sonographically guided anesthetic injection of anterior scalene muscle for investigation of neurogenic thoracic outlet syndrome. *Skelet Radiol*. 2009;38(11):1083–1087.



• **Figure 68.15** Ultrasound guided needle placement for anterior scalene muscle injection. Torriani M, Gupta R, Donahue DM. Sonographically guided anesthetic injection of anterior scalene muscle for investigation of neurogenic thoracic outlet syndrome. *Skelet Radiol*. 2009;38(11):1083–1087.

for the roots of the brachial plexus to pass through the middle scalene muscle. The injected LA may spill through the fascia of the scalene muscles. If this happens, the patient should be discharged with an arm sling. Note that relief is not dependent on blockade of the brachial plexus. A series of injections can be performed two to three weeks apart if the relief is prolonged. Even though the usual duration of relief is days to a week, it may last up to four weeks when a series of injections are performed.[156] If relief lasts only for hours or a few days, either injection of botulinum toxin or resection of the anterior or middle scalene (or both) can be performed. Published doses of botulinum toxin are 12–15 units of botulinum toxin A per muscle. Regarding the results of surgery, a retrospective two-year functional outcome study showed good and fair results in 49% and 35% of patients, respectively.[166] A good response to injection of LA into the scalene muscles correlates with a good outcome after scalenotomy, and first rib resection.[162,167] Relief of pain from scalene muscle injections in patients with TOS is not related to blockade of the brachial plexus.[162]

Rached et al. published a randomized, placebo-controlled, double-blind clinical trial with a parallel group. They concluded that the injection of 0.375% ropivacaine in doses of 2.5 mL in each belly of the anterior and middle scalene muscles, guided by ultrasound, in the treatment of disputed neurogenic TOS, assists in the improvement of function (primary outcome) evaluated for 12 weeks by the disabilities of the arm, shoulder, and hand - DASH scale.[158]

Mashayekh et al. performed CT guided scalene injections, which produced accurate results compared to other techniques of image guided scalene injection.[155] CT guided LA or botulinum toxin injection of the scalene muscle is a novel technique, and they evaluated the outcomes and complications of this procedure in a large group of patients. In this study, 68/83 (82%) of the anesthetic injections into the ASM alone or anterior scalene muscle (ASM)/middle scalene muscle (MSM) together resulted in a positive scalene block, which was higher than that in studies using needle guidance by sonography (11/29, 38%), 11 EMG and fluoroscopy (4/22, 18%), 20 or EMG alone (93/122, 72%) under CT guidance, highlighting that scalene injection is a safe procedure.[155]

Donahue et al. demonstrated a favorable response to sonographically guided BTX injections is associated with favorable surgical outcomes at two years follow up and has a high positive predictive value, suggesting they may help predict surgical outcomes.[154] They used a free-hand technique, with AS being injected lateral-to-medial and PM injected via an oblique approach. BTX type A was reconstituted in 2 mL of preservative-free saline with a fixed dose for all patients: 18 U for AS and 23 U for PM.

Sonographically guided injection of anesthetic into the AS muscle is safe and well tolerated. Sonography allowed precise depiction of AS muscle and intramuscular needle placement. Unintended brachial plexus blocks may occur in up to a third of the procedures.[157] Scalene injection confirms the clinical diagnosis of TOS in patients presenting with typical patterns of pain and paresthesia and helps to identify the relative contribution of TOS when symptoms overlap with another disease. An earlier return to everyday life and work in patients with TOS is possible by combining scalene injection with conservative treatments such as medication.

Summary

Myofascial pain and myofascial pain syndromes are among some of the most common acute and chronic pain conditions. The pathophysiology of myofascial pain includes biomechanical and postural factors that likely interact with neurologic factors, psychological elements including depression and anxiety, and hormonal and nutritional imbalances. These factors (in total or in part) may create peripheral sensitization, autonomic dysregulation, and ultimately, central spinal cord sensitization, which can amplify the symptoms experienced by patients with myofascial pain. Many interventional procedures can be performed in acute and chronic pain settings to address myofascial pain syndromes. Injections can be achieved with or without imaging guidance, such as fluoroscopy and ultrasonography. However, the use of imaging in years past has been recommended to improve patient outcomes and safety. Injections can be performed utilizing no injectate (dry needling) or involve the administration of LAs, botulinum toxin, or corticosteroids. A proper history and physical examination of the patient and imaging studies may help identify the correct myofascial pain syndrome and aid in developing an appropriate treatment strategy for these very common conditions.

Key Points

- A trigger point is the hallmark of myofascial pain syndromes, which may be treated with physical therapy and injections.
- The growing accessibility of ultrasound has improved available options for anesthesia and analgesia to the thoracic region and the piriformis, iliopsoas, and scalene muscles.
- Piriformis syndrome may mimic L5–S1 radiculitis, although the pain originates in the buttock. There are signs and symptoms that aid in the diagnosis of the syndrome. Injections of LA and steroids may ameliorate the pain. If relief from a series of local anesthetic/steroid injections is transient, botulinum toxin can be injected.
- Signs and symptoms of iliopsoas muscle pain are usually nonspecific. Diagnostic/prognostic local anesthetic injections may be performed, followed by botulinum toxin injection.
- The diagnosis of neurogenic TOS can be made from the patient's symptoms, physical examination, electromyographic findings, and imaging (also to rule out other pathologic conditions). LA injections into the anterior and middle scalene muscles are preferably performed under ultrasound guidance. A series of LA injections or botulinum toxin injections may be performed; first rib resection and scalenectomy may result in long-term benefits.
- ESPB is a regional technique first described in 2016 that is used to provide analgesia to the thoracic wall. Although the mechanism of LA spread and consistency of analgesia achieved are still under investigation, it is an attractive option because it can be performed on fully anticoagulated patients in whom neuraxial techniques are contraindicated.
- Truncal fascial plane blocks such as PECS II, SAPB, QL block are other ultrasound guided options for providing analgesia to the thorax.
- The injections should be part of a multi-disciplinary treatment program that includes physical therapy.

Suggested Readings

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69

Minimally Invasive Procedures for Vertebral Compression Fractures

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One in two women and one in five men aged >50 years will experience an osteoporotic fracture. These can result in substantial patient pain, morbidity, and healthcare utilization. A new osteoporotic vertebral fracture occurs every 22 s; 1.4 million occur worldwide every year.[1] The majority are asymptomatic or result in tolerable symptoms, with only a third of patients with new fractures seeking medical attention.[2] For the vast majority, acute back pain symptoms subside over a period of six to eight weeks as the fracture heals.[3]

Vertebroplasty and kyphoplasty are minimally invasive image-guided procedures that involve the injection of polymethylmethacrylate (PMMA) into a fractured vertebral body (Fig. 69.1–69.2). Most of these vertebral augmentation procedures are performed for a small subset of patients with symptomatic osteoporotic compression fractures that fail to respond to conservative medical therapy. Failure of medical therapy is variably defined but can be considered if pain persists at a level that severely compromises mobility or activities of daily living despite analgesic therapy or if unacceptable side effects such as confusion, sedation, or constipation occur as a result of medication doses required to reduce pain to tolerable levels. The first report of vertebral augmentation, published in 1987, was for neoplastic disease.[4] As survival rates in cancer patients continue to improve, symptomatic neoplastic vertebral fractures or neoplastic vertebral tumors have increased in prevalence. A selected sub-group of these patients, particularly those with symptomatic fractures from multiple myeloma and metastasis that fail to respond to conservative therapy, also benefit from vertebral augmentation.[5] The primary goal of vertebral augmentation is pain relief and enhanced functional status with the secondary goals of vertebral body stabilization in cases of fracture. Emerging population level evidence suggests a mortality benefit in patients treated with vertebral augmentation compared to conservative therapy.[6]

Indications and contraindications for vertebral augmentation are summarized in Box 69.1.

Conservative Medical Therapy

Conservative therapy aims to reduce pain (with analgesics and/or bed rest), improvement in functional status (with orthotic devices and physical therapy), and prevention of future fractures (with vitamin D and calcium supplementation and bisphosphonate therapy).

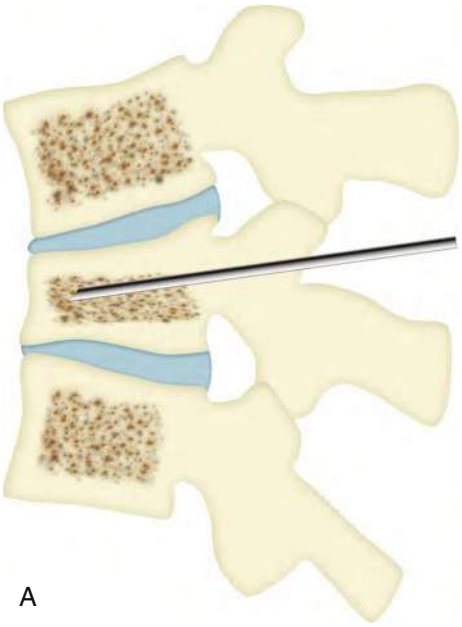
While conservative management for those with mild pain and no limitation of function is appropriate, conservative treatment for those with more severe pain or limitation of function is not benign. In this cohort, conservative therapy often involves a period of bed rest, which may lead to undesirable side effects such as bone mass and muscle strength loss, decubitus ulceration, and venous thromboembolic disease (VTE), all of which can prolong the recovery period and result in loss of independence. Bone loss occurs at approximately 2% per week,[7] muscle strength reduces by 10%–15%,[8] and infectious complications can lead to septicemia and osteomyelitis. Reduced lung capacity can also predispose patients to pneumonia. Moreover, the presence of fracture or malignancy combined with bed rest elevates the risk of VTE in this cohort. Overall, complications of prolonged bed rest, combined with opioid narcotic use and associated side effects, can result in a vicious cycle of physical deconditioning, poor nutrition, and a subsequent increased risk of vertebral insufficiency.

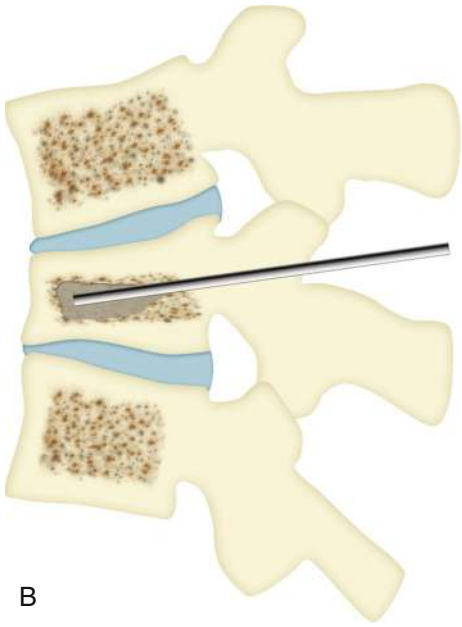
Technical Aspects

The evaluation of patients for vertebral augmentation should identify patients likely to benefit from vertebral augmentation, as well as screen for contraindications. The decision to proceed with treatment must be based on a good history, physical examination, appropriate laboratory evaluation, and imaging, as summarized in Box 69.2.

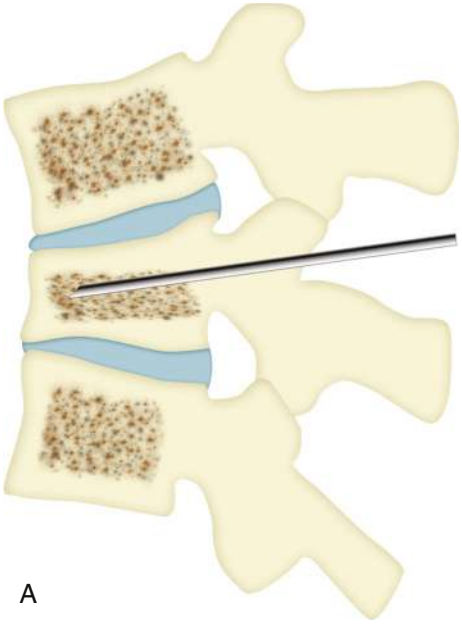
Sedation

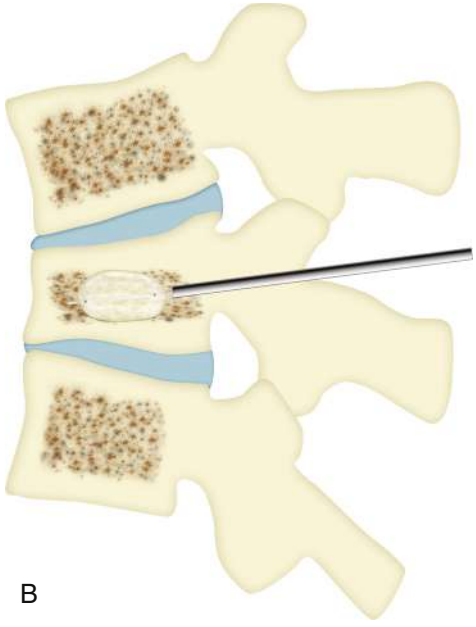
Analgesia is typically necessary for vertebroplasty and kyphoplasty. In most cases, this is achieved with a combination of local anesthetic (e.g. lidocaine with bicarbonate or bupivacaine) and moderate sedation (intravenous midazolam and fentanyl). In some cases, the preferred approach is to utilize general anesthesia to provide adequate comfort and safety, particularly in patients who a However, having the patient awake allows feedback (e.g. increasing pain and neurologic dysfunction) that can alert the operator to potential complications. In all cases, continuous monitoring was performed with a minimum electrocardiogram (ECG), blood pressure measurements, and pulse oximetry. Drug delivery and monitoring are performed by anesthesiologists, nurse anesthetists, or certified nursing personnel. In patients with substantial preexisting respiratory or cardiac disease, an anesthesiologist can be asked to evaluate the patient and determine if monitored anesthesia care is warranted. The patient should not eat or drink for at least 4–6 h prior to the procedure.

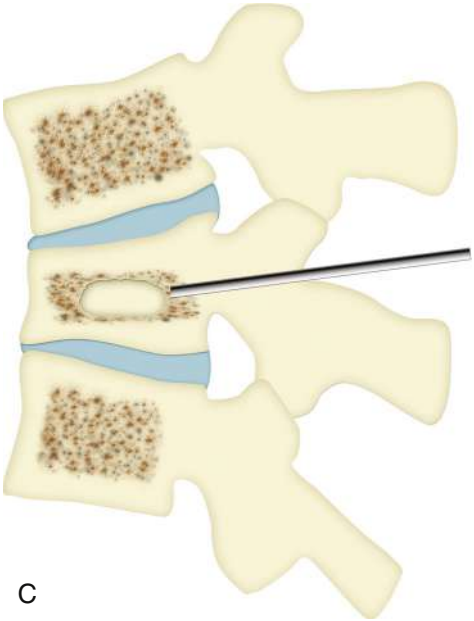


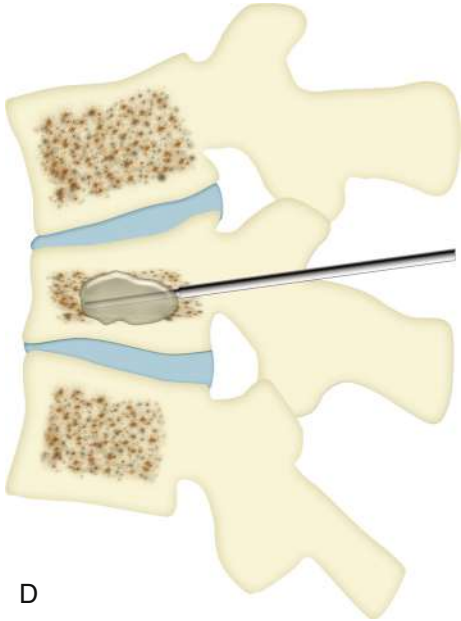


• **Figure 69.1** Vertebroplasty involves the insertion of a needle into the vertebral body **(A)** with subsequent delivery of cement **(B)** into the vertebral body.









• **Figure 69.2** Kyphoplasty. Once vertebral body access is achieved **(A)**, the inner stylet is removed, and a balloon tamp inflated within the vertebral body **(B)** to create a cavity within the bone **(C)** into which cement is delivered **(D)**.

• BOX 69.1 Indications

1. Treatment of symptomatic osteoporotic vertebral body fractures that are refractory to conservative medical therapy
2. Treatment of symptomatic vertebral bodies that are refractory to medical therapy weakened or fractured because of neoplasia

Absolute contraindications

1. Active systemic infection, in particular, spinal infection
2. Uncorrectable bleeding diathesis
3. Insufficient cardiopulmonary health to safely tolerate sedation or general anesthesia
4. Myelopathy resulting from fracture retropulsion or epidural tumor extension
5. Known allergy to bone cement

Relative contraindications (should only be treated by experienced practitioners)

1. Marked loss of vertebral body height (greater than 75% height loss)
   a. Makes the procedure more difficult because there may be little space for cannula placement.
2. Vertebroplasty above T5
   a. Challenges because of the small size of the vertebral bodies and pedicles. The shoulders often limit fluoroscopic imaging at these levels.
3. Severe osteopenia resulting in poor visualization of osseous structures on fluoroscopy
   a. Increases the risk of improper needle placement and cement leakage. This can be overcome with computed tomography (CT) guidance.
4. Disruption of the posterior cortex
   a. Increases the risk of posterior cement leakage and, therefore, the risk of the spinal cord or nerve root compression. This phenomenon is frequently observed in burst fractures and neoplasms. The integrity of the posterior cortex was best evaluated using CT scanning.
5. *Substantial canal narrowing* (without neurologic dysfunction)
   a. Increases the risk that even a small amount of cement leakage will produce neurologic compromise.
6. Retropulsion of fracture fragments
   a. Risk of further canal compromise with vertebral augmentation, particularly if the posterior vertebral body wall is unstable.
7. Epidural extension of tumor
   a. Pathologic fractures result in significantly higher rates of spinal canal leakage than osteoporotic fractures.

Patient Positioning

Prone or oblique prone is the ideal patient position for thoracic and lumbar procedures. Besides the clear advantage of easy access, this position with proper cushion support under the upper chest and lower abdomen maximizes extension of the fractured segments, promoting kyphosis reduction.[9] The patient's arms should be placed sufficiently toward the head to keep them out of the path of the fluoroscope. Analgesia should be considered prior to placement on the table, as this part of the procedure may be quite painful. Care must be taken when transferring patients who are aged, osteoporotic, or with myelomatous infiltration, as this may result in new rib or vertebral fractures.

Antibiotic Prophylaxis and Skin Preparation

The risk of infection is minimized by using standard operating room guidelines for sterile preparation of the skin, draping, operator scrub, and sterile gowns, masks, and gloves. There is little data to support or oppose antibiotic administration, but there are reports of spine infections after these procedures,[10,11] and the presence of PMMA makes these infections difficult to treat successfully. We routinely use antibiotic prophylaxis prior to skin incision, which includes intravenous antibiotics such as cefazolin (1 g) or clindamycin (600 mg if there is a penicillin allergy). Alternatively, polymethylmethacrylate (PMMA) may be mixed with an antibiotic, such as tobramycin (1.2 g) or vancomycin, as the cement is being prepared; this practice has diminished in favor of intravenous antibiotics.

Needle Placement

The most important aspect of needle placement is to keep the needle trajectory lateral to the medial cortex and superior to the inferior cortex of the pedicle. This prevents entry of the needle into the spinal canal or neural foramen. The needle may be placed via a transpedicular or parapedicular approach. The transpedicular approach takes the needle from the posterior surface of the pedicle, through the length of the pedicle, and into the vertebral body. The long intraosseous path protects the postganglionic nerve roots and other soft tissues. However, the pedicle configuration can limit the ability to achieve a final needle tip position near the midline. The parapedicular approach takes the needle along the lateral surface of the pedicle, penetrating the pedicle along its path or the vertebral body at its junction with the pedicle. This approach may permit a more medial tip placement, which can be useful during the treatment of levels with anatomically small pedicles, particularly in the thoracic spine.

For either approach, there are multiple potential image guidance strategies, an anteroposterior view or an end on ("down the barrel") view, with the latter technique employing ipsilateral oblique rotation of the image intensifier to place the fluoroscopy beam and needle tract parallel to each other.

1. Rotate the image intensifier (II) to a true AP position by aligning the spinous process midway between the pedicles (Fig. 69.3).
2. Change the craniocaudal angulation by bringing the pedicles to the midportion of the vertebral body. A lateral fluoroscope was used to aid in the determination of the correct craniocaudal adjustment required.
   a. For the end on view, rotate the II approximately 20° ipsilateral to the target pedicle so that the medial cortex of the pedicle is at the middle third of the vertebral body. The vertebra adopts the "Scotty dog" configuration. Place the needle so that it is "end on" to the image intensifier and appears as a dot.
3. Plan the trocar trajectory. For the AP and partial ipsilateral oblique views, the trocar entry position should be at the 3 o'clock position of the right pedicle or the 9 o'clock position of the left pedicle for the transpedicular approach. The view should be centered within the circle formed by the cortex of the pedicle. For the parapedicular approach, an entry position just lateral to the 3 or 9 o'clock positions of the pedicular cortex is the best.
4. The skin and periosteum were anesthetized with subcutaneous lidocaine or bupivacaine using a 22-gauge needle following the planned trajectory. A smaller gauge needle was used to assess and adjust the planned trajectory.
5. A small vertical skin incision was made (allowing easier craniocaudal needle angulation) and place the 11 or 13-gauge diamond-tip needle stylet (sheathed in a cannula).
6. The needle was advanced to the bone surface, making small corrections in the craniocaudal plane using the true lateral view (care is needed to angle the II so that a true lateral view

• BOX 69.2 Pre-procedural Workup

Identify those patients who will likely benefit from vertebral augmentation.
Screen for absolute contraindications.
Document failure of conventional medical therapy.

Symptoms

- Fractures may occur with little or no trauma.
- Deep pain with sudden onset
- Midline location
- Exacerbation by axial mechanical loading (worsening with standing or weight-bearing and often at least partially relieved by recumbency)
- Exacerbation by motion (especially flexion)
- Referred lateral radiation in a dermatomal pattern because of foraminal narrowing may be present.

Signs

- Point tenderness at the spinous process of fractured vertebra Local signs may be absent.
- Per Rad et al. up to 30% of patients may have subjective off-midline pain or tenderness over non-target vertebrae and still gain significant benefit.*
- Localization to a specific level if possible is important in targeting treatment in patients with multiple compression fractures, some of which may be healed and do not require treatment. In difficult cases, examination can be performed with fluoroscopic assistance to localize the pain to a specific anatomic level.
  Assess lower extremity neurologic function.

Laboratory evaluation

- Screening for infection, coagulopathy, and metabolic abnormalities
- Additional tests such as the performance of a urinalysis, electrocardiogram (ECG), and/or chest radiography are left to the discretion of the practitioner.

Imaging

- The role is to confirm the clinical diagnosis, identify and assess the acuity of the painful fracture, identify potential difficulties, and plan the procedure.
- Fracture imaging can be performed with magnetic resonance imaging (MRI) or nuclear scintigraphic bone scan to correlate symptoms with the vertebral level in question and confirm the acuity of the fracture.
- MRI sequences include short tau inversion recovery or T2-weighted sequences with fat saturation. These sequences identified marrow edema, distinguishing between acute and chronic fractures. MRI also distinguishes between benign osteoporotic and pathologic fractures, and assesses the degree of fracture retropulsion, epidural tumor extension, spinal canal compromise, and compression of the spinal cord or nerve roots. Fracture clefts appear as a linear band of T1 hypointensity and T2 hypo- or hyperintensity within the vertebral body. Fluid signal intensity should be interpreted with caution, as some studies demonstrate persistent signals many months after the known incident fracture.
- Nuclear scintigraphic bone scan or single-photon emission computed tomography (SPECT) combined with CT are the tests of choice. Acute fractures will take up the injected ^{99m}Tc-MDP tracer at much higher concentrations; CT evaluates the bony integrity and spinal contents. In patients with pathologic fractures, CT also helps define the extent of sclerosis and posterior wall osteolysis, which predicts increased technical challenges associated with the procedure.

*Rad AE, Kallmes DF. Pain relief following vertebroplasty in patients with and without localized tenderness on palpation. *AJNR.* 2008;29:1622-1626.

is obtained). For the parapedicular approach, the position at which the bone is encountered (i.e. at the junction of the pedicle and vertebral body) is more anterior in the lateral view.

7. Once in the bone, advance the needle with a drilling motion and controlled forward pressure or by carefully tapping the needle handle with an orthopedic mallet.
8. Kept II with a true AP view for needle advancement, unless the end on view is used, where the needle is kept as a dot through the initial placement through the pedicle. The needle must remain lateral to the medial cortex of the pedicle until it traverses the entire pedicle on the lateral view.
9. Once the needle has traversed the pedicle, the diamond-tip needle can be replaced with a straight bevel-tip needle or curved needle for better maneuverability (Fig. 69.4). The needle was advanced further using the lateral view to the anterior one-third to one-quarter of the vertebral body.

Additional Steps For Kyphoplasty

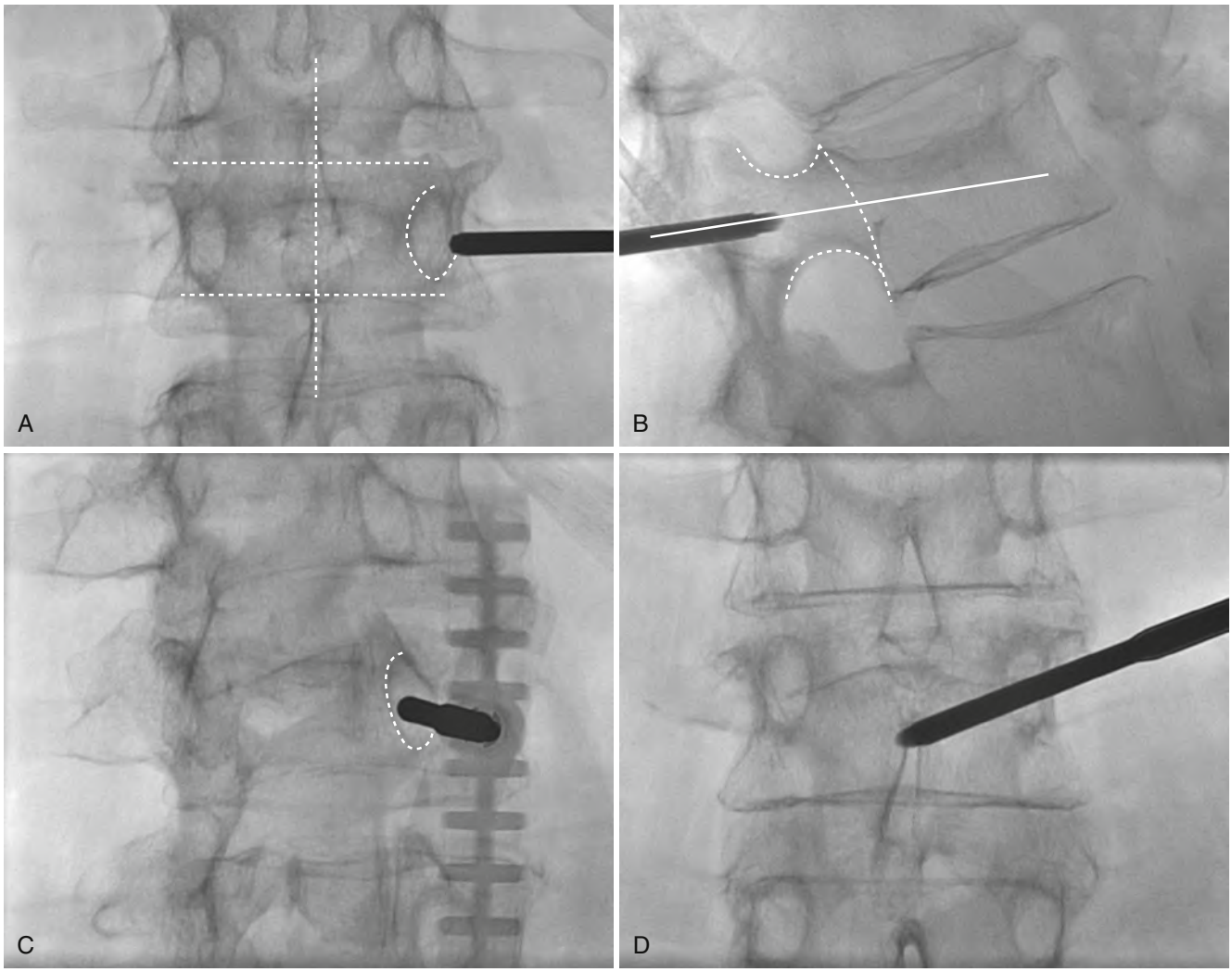
For vertebroplasty, PMMA is delivered through the cannula after the needle placement described above. Kyphoplasty involves additional steps of balloon tamp insertion and inflation to create a cavity within the bone (Fig. 69.5). For kyphoplasty, the cannula was pulled back to the posterior aspect of the vertebral body to allow for the insertion of the balloon tamp. After the needle stylet was removed, the balloon tamp was inserted through the cannula and slowly inflated with iodinated contrast. The balloon was attached to a locking syringe using a digital manometer (Fig. 69.6). Monitor the inflation both with the pressure transducer and intermittent fluoroscopy. Continue inflation until one of two conditions is met: the system reaches significant pressure or maximum balloon volume, or further inflation results in patient discomfort if performed with sedation. Balloon placement can be either unipedicular or bipedicular. Deflate and remove the balloon

Cement Placement

The consistency of the cement, when ready for injection, was similar to that of toothpaste. Wong et al. recommended a drip test in which the cement should ball up at the end of the needle and not drip downward, resulting in a cement that is slightly more viscous than toothpaste.[12] The working time varies from 10–20 min, depending on the temperature and the specific PMMA formulation being used. A variety of delivery systems are available for cement. These systems vary from a few 1 cc syringes with a spatula and a mixing bowl to self-contained delivery devices with automatic mixing. A screw-syringe injector with long, flexible delivery tubing has the advantage of minimizing radiation exposure to the operator.[13]

Vertebroplasty

- After removing the needle stylet, the cannula was filled with saline to prevent pressurized injection of air and air embolus. The delivery system is connected to the cannula, and the cement is injected slowly.
- The monitor was carefully monitored with fluoroscopic imaging to ensure that the cement remained within the vertebra.



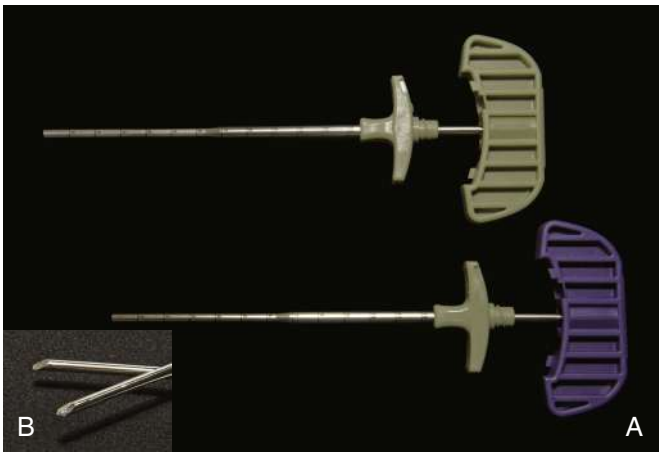
• **Figure 69.3** Initial positioning for needle trajectory for transpedicular approach. **(A)** Anteroposterior (AP) fluoroscopic image. The image intensifier is first rotated to a true AP position, aligning the spinous process midway between the pedicles (*vertical dotted line*). The craniocaudal angulation is changed to bring the pedicles to the midportion of the vertebral body (*horizontal dotted lines*). **(B)** Lateral fluoroscopic image. The image intensifier is rotated to a true lateral position by overlapping the cortices of both pedicles and ensuring that the posterior margin of the vertebral body is aligned (*dotted lines*). Note that the entire needle trajectory within the vertebral body should be considered during initial transpedicular access for optimal final needle position (*solid line*). **(C)** Near "end on" projection during needle placement with preservation of the medial and inferior cortices of the pedicle. Note that the "T-grip" needle handle can obscure bony landmarks, and slight II rotation may be required. **(D)** Midline needle position achieved with unilateral transpedicular approach, achievable with larger target pedicles, typically in lumbar vertebrae.

Posterior or posterolateral leakage could result in irritation or damage to the spinal cord or nerve roots and should be avoided. New pain with a different character should prompt immediate procedural pauses and additional views.

- The endpoints for cement injection include the passage of cement beyond the marrow space and/or cement reaching the posterior quarter of the vertebral body on the lateral projection. In the case of cement leakage, one may wait for 1–2 min to allow the cement to harden and then reinject to see if the cement is redirected within the vertebral body.[14] Ideally, the cement will extend across the midline and to the opposite pedicle by the end of the injection. However, the optimal amount of cement volume injection remains controversial.
- The final portion of the cement was delivered by inserting the needle stylet. Alternatively, the cement may be allowed to harden, and the needle is removed with a gentle rocking motion to ensure that the cement within the cannula separates at the cannula tip. However, care should be taken not to fracture the vertebral pedicle.

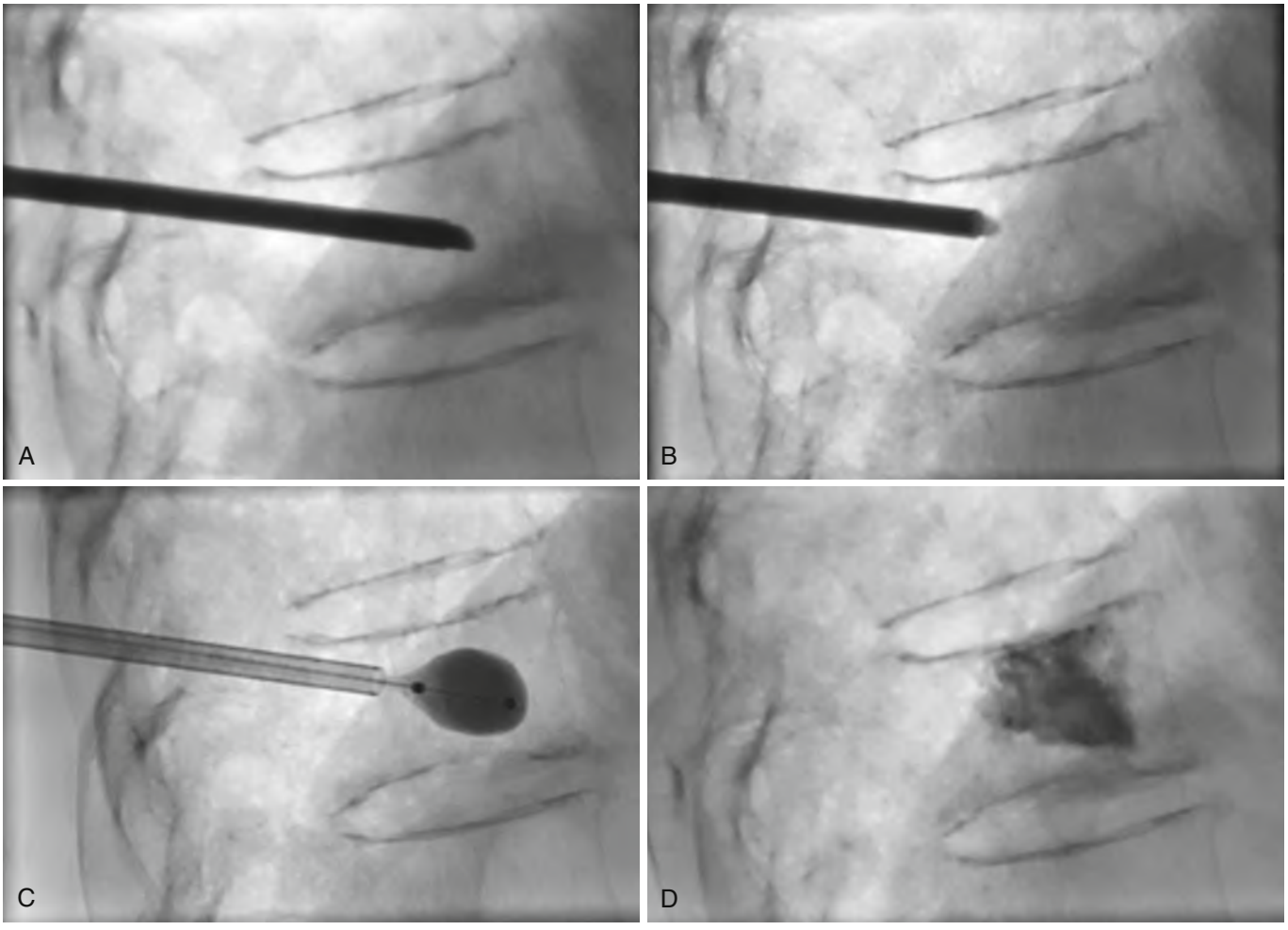
Kyphoplasty

- The cavity created by the balloon tamp allows for the injection of a more viscous cement than that typically used for vertebroplasty. The cavity and more viscous cement theoretically minimize the risk of cement extravasation. Sufficient time is allowed for the cement to reach a doughy consistency, with loss of the "sheen" of the initially mixed cement.
- Many practitioners use manual bone filler devices to inject cement, although injector systems can be used. The delivery



• **Figure 69.4** Photographs of typical vertebroplasty needles. **(A)** Typical co-axial vertebroplasty needle—the inner stylet locks into the outer cannula. Note the large handles to facilitate insertion and removal from the bone. Manufacturers may use different colored or marked handles to indicate the type of needle tip (magnified in **B**) The beveled tip needle can be used to facilitate needle direction along a desired trajectory.

• **Figure 69.6** Balloon kyphoplasty. The balloon is attached to a digital manometer that allows assessment of balloon pressure. Note the long flexible tubing that allows the operator's hands to remain out of the primary radiation beam during the fluoroscopic assessment of balloon inflation.



• **Figure 69.5** Additional steps for kyphoplasty. **(A)** Lateral fluoroscopic image. The unipedicular needle has been placed into the anterior thirds of the T10 vertebral body. **(B)** The needle is withdrawn to the posterior third of the vertebral body and the inner stylet removed. **(C)** The balloon tamp is introduced into the needle tract and inflated to create a cavity within the bone. **(D)** Cement opacifies both the cavity and extends into adjacent trabecular bone.

system was connected to the cannula, and the cement was slowly injected under fluoroscopic guidance. The cement fills the cavity from anterior to posterior, matching or slightly exceeding the volume of the inflated balloon tamp.

Controversies and Special Topics

Bipedicular Versus Unipedicular Approach

Vertebroplasty and kyphoplasty can be performed with the placement of bilateral needles or a single needle.[15] In either case, the goal is to place cement across the midline within the vertebral body—we use the placement of PMMA to the opposite pedicle as our general landmark. Therefore the use of a single needle with a relatively medial needle tip position is sufficient in many cases. If a unilateral approach is attempted during kyphoplasty and balloon expansion does not cross the midline, a second system may then be placed on the other side depending on the distribution of the cement fill. In many cases, the cement fill will continue across the midline, obviating the need for a second needle. Moreover, hemivertebral fill (cement traverses <10% of the contralateral unfilled vertebra) has been shown to reduce pain and improve function without increasing the risk of fracture.[16]

There is no statistically significant difference in pain relief achieved between the unipedicular and bipedicular vertebroplasty,[17] or kyphoplasty.[18] There are advantages to each approach. The advantages of a unipedicular approach include a decrease in procedure time and elimination of the risk associated with a second needle placement. A unipedicular approach is also associated with lower rates of cement leakage.[19] The major advantage of a bipedicular approach is that access is typically transpedicular with a less aggressive lateral-medial approach that may result in less paravertebral vessel and nerve injury and a potential biomechanical advantage to bilateral cement delivery.

Volume of Cement Injection

The optimal volume of cement is a matter of controversy, with some practitioners advocating injection of maximal amounts of cement to completely fill the vertebral body and others advocating lower cement volumes with an emphasis on safety. The theoretical goal of more complete filling is to achieve restoration of biomechanical strength within the vertebral body to prevent re-fracture without creating excess stiffness that may be transmitted to the adjacent levels. Based on an in vitro biomechanical study, Mathis et al. recommend cement filling of 50%–70% of the residual volume of the vertebral body.[20] However, much smaller amounts of cement (as little as 0.5 cc) appear to result in similar clinical outcomes, in terms of the primary goal of pain relief, when compared to larger volume injections, with no association between the volume of cement injected and the clinical outcomes of pain and medication use.[19] The decreased risk of cement extravasation with smaller volume injections and meticulous attention to the end of injection criteria outlined above recommends a smaller cement volume approach.

Vertebra Plana

When the vertebral body loses 70% of its original height, safe needle placement becomes a challenge. According to Stallmeyer et al., at least 8 mm of residual height is required for cannula placement.[21] The vertebra plana often adopts a bow-tie configuration, where the center is compressed the most. This usually requires a lateral needle position with the placement of bilateral needles.[22] Only a small amount of cement is needed to achieve pain relief.[23] If there is a cystic cleft within the fracture (Kummel disease), the needle may be placed near the midline within the cleft with the hopes of height expansion during needle placement and cement injection.

Fractures With Intraosseous Vacuum Phenomenon (Kummel Disease)

The intraosseous vacuum phenomenon is thought to be related to osteonecrosis. A fluid-filled cleft seen on magnetic resonance imaging (MRI) is an equivalent finding. Pain in this setting is believed to arise from the motion between the unhealed fracture fragments. Sometimes, this motion can even be seen under fluoroscopy as the height of the vertebral body changes with respiration. Prone positioning during the procedure promotes height restoration because of traction placed across the vertebral body. The needle should be placed into or as close to the cleft as possible so that the cement will fill the cleft. Vertebral augmentation yields significant rates of pain relief in the setting of intraosseous vacuum phenomenon,[24,25] and in our experience, can provide considerable height restoration. Keeping the patient prone for 15–20 min after the cement injection is important to allow the cement to harden within the cleft before moving the patient off the fluoroscopy table.

Malignant Fractures With Posterior Wall Osteolysis or Epidural Tumor Extension

Although vertebral augmentation may be performed in the setting of posterior wall osteolysis or epidural tumor extension, there should be a heightened awareness of the potential neurologic complications related to the epidural extension of cement or posterior displacement of the tumor. In a study of 51 patients with a vertebral lesion with epidural extension treated with vertebroplasty, 30% had pre-procedural symptoms of partial or complete cord compression/cauda equina syndrome.[26] These patients were terminally ill and not surgically decompressed because their paraplegia was deemed irreversible (present for greater than one month or associated with spinal cord atrophy) or their general condition contraindicated the surgery. Although no further clinical deterioration was observed in this subgroup after vertebroplasty, one of the 36 patients without neurologic symptoms developed cauda equina syndrome two days after vertebroplasty and required surgical decompression.[26] Any cement leakage (as detected on post-procedure computed tomography [CT]) occurred in 62%, with half of these leaks into the epidural space. Importantly, cement extension beyond the confines of the vertebral body but within the epidural tumor was still classed as a leak.[27] Nonetheless, the case mentioned above was the only symptomatic cement leak. No systemic complications were observed. Analgesic efficacy, based on 50% or greater improvement in pain as compared with baseline, was impressive—94% (48 of 51 patients) at day one, 86% (31 patients) at one month, 83% (19 patients) at six months, and 92% (11 patients) after one year (data are from surviving patients).[26] Safeguards to prevent complications in this cohort included performing the procedure with the patient awake (new pain may be the first sign of dangerous cement leakage) and more-modest cement injection than routine cases. Limiting the cement to the anterior two-thirds of the vertebral body may be a good rule of thumb, as well as injection of thicker cement, which may reduce the risk of epidural cement leakage.[28]

Safety of Multilevel Treatment

Patients presenting with vertebral augmentation may have multiple fractures that require treatment. Ideally, all levels are treated at one time. However, treating an excessive number of levels in a single session raises many concerns, including PMMA toxicity, difficulty for the elderly to lay prone and cooperate for the extended amounts of time this would require, discomfort post-procedurally related to multiple needle placements, and fat emboli being extruded from the marrow during the cement injections. There have been two reported deaths in patients who received vertebral augmentation at eight or more levels.[29] While there are no established guidelines, a good rule of thumb is to treat a maximum of three levels per session.[30,31]

Outcomes

The mechanism by which vertebroplasty and kyphoplasty relieve pain is uncertain.[32] Hypotheses include mechanical stabilization of mobile fracture fragments, thermal or chemical neurolysis, or inherent tumoricidal or cytotoxic effects on malignant fractures. A cadaveric study has also demonstrated new bone formation after PMMA injection.[33]

There are now four placebo-controlled randomized controlled trials published in the *New England Journal of Medicine, The Lancet*, and the *British Medical Journal*. These studies have demonstrated mixed results regarding pain outcomes in vertebroplasty. These trials employed a sham procedure in the placebo arm. This involves the injection of local anesthetic into the periosteum of the pedicle,[34] local anesthetic injections combined with the passage of a 13-gauge needle to rest on the lamina,[35,36] or subcutaneous local anesthetic only with needle insertion and tapping on the needle with manual skin pressure.[37]

Two highly publicized placebo-controlled randomized clinical trials in the *New England Journal of Medicine* found that there was no significant reduction in pain or pain-related disability in patients undergoing vertebroplasty compared to the sham procedure.[34,36]

The INVEST trial (NEJM) included 131 patients, with 68 patients randomized to vertebroplasty and 63 to the sham procedure.[34] Although, at one month, there was a trend toward a higher rate of clinically meaningful improvement in pain (30% decrease from baseline), there was no statistical difference in pain scores, back pain-related disability, or quality of life.[34] Buchbinder et al. (NEJM) studied 78 patients, with 38 patients randomized to vertebroplasty and 40 to the sham procedure.[36] After the procedure, both groups had similar improvements in pain, physical functioning, and quality of life. There were no significant differences between the groups at one week, one month, three months, and six months of follow up.[36]

These reports contrast with retrospective case series and conservative controlled trials that had documented impressive rates of pain relief from these procedures.[38–41] The NEJM trials were criticized for potentially including patients with chronic fractures of up to 12 months in duration. The average back pain duration was 18 weeks in the INVEST, with one-third of all patients randomized having pain for greater than six months. The Buchbinder trial included four patients randomized after six months. In the INVEST trial, marrow edema on MRI or increased uptake on bone scanning was only required for fractures of an uncertain age (rate of usage was not reported); in the Buchbinder trial, MRI demonstrating marrow edema and/or a fracture line was required. However, the determination of bone marrow edema was not described. Further criticisms include inconsistent use of physical examination, difficulties in recruitment, and the absence of a control group without intervention.

Subsequently, the VERTOS II investigators[40] performed a blinded randomized trial randomizing 202 patients with severe back pain for six weeks or less, focal tenderness at the fracture level, and MRI demonstrated bone edema, equally into vertebroplasty or conservative arms. All patients were prescribed analgesics that were individually titrated, bisphosphonates, calcium, and vitamin D supplements. Vertebroplasty was performed at a mean of 5.6 weeks after symptom onset. There were statistically significant reductions in mean visual analog scores (VAS) in favor of vertebroplasty at one month ($p<0.0001$), with the benefit persistent at one year ($p<0.0001$).[40] There were significant reductions in the use of drugs compared with conservative treatment at one day ($p<0.0001$), one week ($p=0.001$), and one month ($p=0.033$).[40] Moreover, significant pain relief (VAS reduction of ≥ three points) was achieved earlier and in more patients after vertebroplasty (29.7 days; 95% confidence interval [CI] 11.45–47.97) than with conservative treatment (115.6 days, 95% CI 85.87–145.40).[40]

The Vertebroplasty for Acute Painful Osteoporotic Fractures (VAPOUR) trial published in 2016 compared early vertebroplasty with sham procedure for patients with severe acute pain.[37] Forty-four percent (44%) of patients achieved the primary outcome of a numerical rating scale of less than four by 14 days compared to 21% in the sham group ($p=0.011$). This treatment effect was durable for six months. Additionally, there were greater reductions in the Roland-Morris Disability Questionnaire (RDQ) and QUALEFFO scores favoring vertebroplasty. Compared to the earlier INVEST and Buchbinder et al. a higher proportion (57%) of patients were hospital inpatients, with most fractures being less than six weeks old, 80% of which were less than three weeks old. In addition, the average PMMA volume injected was higher than in earlier trials, although the correlation between cement volume and pain outcomes remains a point of contention. The median length of admission was reduced by 5.5 days after vertebroplasty. Anatomic outcomes were also superior, with 30% greater vertebral height preservation compared with the sham procedure.

VERTOS IV, published in 2018, is the most recent randomized controlled trial (RCT) comparing vertebroplasty for vertebral fracture with a sham procedure.[42] Similar to Buchbinder et al. and INVEST trials, there was no overall benefit in pain outcomes with vertebroplasty compared to the sham procedure. The trial included patients with fractures of up to nine weeks old. Both groups had clinically and statistically significant reductions in pain and improved quality of life up to 12 months. However, there were no statistically significant differences between the groups. VERTOS IV only included outpatients, with a mean fracture duration of 6.1 weeks, compared to 2.1 weeks for the VAPOUR trial.[37] Furthermore, only 25% of fractures in VERTOS IV were less than four weeks old. This implies that fracture chronicity and severity are important in patient selection. In this data set, vertebroplasty was not a risk factor for further vertebral fractures.[42]

The FREE trial was another large trial supporting the efficacy of vertebral augmentation.[43] A total of 300 patients were randomized to receive kyphoplasty (n=149) or conservative therapy (n=151). Fractures had a minimum height loss of 15% and MRI evidence of edema. Although both osteoporotic and malignant fractures were included, 96% of fractures were related to primary osteoporosis. At randomization, fractures were a mean of six weeks

old. Kyphoplasty was performed at a mean of seven days after randomization, and patients with fracture ages greater than three months were excluded. The primary outcome measure was the mean short-form (SF)-36 Physical Component Summary (PCS) scale, a validated global quality of life measure weighted on physical abilities.[43] There were statistically significant improvements in the SF-36 PCS scores in favor of kyphoplasty at one month (p<0.0001) and 12 months (p=0.0004). There were greater reductions in the RDQ scores in favor of kyphoplasty at one month (p<0.0001) and 12 months (p=0.0012).[43] Patients in the kyphoplasty group also had greater reductions in back pain scores, lower rates of narcotic analgesic use, and fewer days of restricted activity compared to those managed with conservative therapy.[43] By 12 months, the differences between the conservative therapy and kyphoplasty groups were diminished, most likely because of fracture healing.[43]

Further RCT evidence comes from the Cancer Patient Fracture Evaluation (CAFE) study that reported the benefit of kyphoplasty over conservative therapy for malignant painful vertebral compression fractures.[5] CAFE recruited 134 patients with malignant fractures at 22 sites in Europe, the USA, Canada, and Australia. Approximately 50% of patients had breast, lung, or prostate cancer metastasis, and 40% had multiple myeloma-related fractures. Patients with osteoblastic tumors, primary bone tumors such as osteosarcoma, or plasmacytoma at the index compression fracture were excluded. Patients were randomly assigned to either kyphoplasty (n=70) or conservative therapy (n=64). The median estimated symptomatic fracture age was 3.5 months (IQR 1.2–6.8); 87 of 129 patients had edema on MRI. The primary endpoint was back-specific functional status, as measured by the RDQ at one month. There was a statistically significant reduction in the RDQ scores in favor of kyphoplasty at one month (p<0.0001).[5] The mean RDQ score in the kyphoplasty group reduced from 17.6 at baseline to 9.1 at one month; the mean score in the control group changed from 18.2–18.0; the kyphoplasty treatment effect on RDQ was -8.4 points at one month (95% CI -7.6 to -9.2; p<0.0001). Patients in the kyphoplasty group also had greater reductions in back pain, and both groups had a baseline mean back pain score of 7.3; the mean score at seven days was 3.5 compared with 7.0, in the conservative arm (p<0.0001), which remained significant at one month (p<0.0001). In addition, there were significant reductions in analgesic use, days of bed rest, improvement in quality of life (measured by SF-36 PCS), and Karnofsky performance status in the kyphoplasty group compared to the conservative arm. These improvements in pain, overall functional status, and quality of life continued for 12 months of the study period.[5]

Concerning long term outcomes, there are few data. Two-year outcome data from the FREE trial revealed that although there were no statistically significant differences in the SF-36 PCS or RDQ scores at 24 months, there remained a statistically significant reduction in back pain scores for patients in the kyphoplasty arm compared to conservative therapy at 24 months (p=0.009).[44] A similar benefit was also reported at 36 months following kyphoplasty in a smaller prospective non-randomized study of 60 patients.[45]

For the prevention of height loss, VERTOS IV demonstrated that vertebroplasty is protective, with significant further vertebral height loss seen in 8% in the vertebroplasty group versus 45% in the sham group (p=0.001) (odds ratio=9.84 [4.08–23.73]).[42] This has implications for further morbidity in an otherwise susceptible elderly population.

For height restoration, the results are less dramatic. Studies have shown that the magnitude of partial height restoration after vertebroplasty ranges from 2.5–8.4 mm and is similar to that reported after kyphoplasty.[46] However, many of these studies did not report the incidence of fracture clefts. Overall, height restoration appears to relate to the dynamic mobility of fracture fragments from the presence of a fracture cleft.[47] Dynamic mobility refers to a change in vertebral body height during changes in position, typically an increase in vertebral body height with supine or prone positioning compared to the erect position, which typically occurs in fractures at the thoracolumbar junction (T11–L1), where the relatively fixed thoracic spine joins the more mobile lumbar spine. A study of 65 vertebral compression fractures referred for vertebroplasty revealed dynamic mobility in a third of treated levels.[48] All fractures that were mobile had a fracture cleft, and all fractures that were fixed did not have a fracture cleft. Fractures that were mobile had an average absolute increase of anterior vertebral height of 8.4 mm (range, 2.0–17.4 mm) and decreased kyphosis angle of 7.2° (40%) after vertebroplasty. There was no height restoration or kyphosis correction in fixed fractures.[48] In general, restoration of vertebral body height and kyphosis correction may be desirable to improve postural endurance, reduce abdominal crowding, and improve overall pulmonary capacity. However, it remains unclear whether these results have clinical significance.[46]

Mortality Benefit

Osteoporotic vertebral compression fractures can result in deformity and have been associated with decreased pulmonary function as well as increased hospitalization and mortality.[49,50]

Several studies have investigated the potential for mortality benefit in patients undergoing vertebral augmentation.[51–53] A recent meta-analysis of more than two million patients with osteoporotic vertebral compression fractures demonstrated the benefit of vertebral augmentation over conservative therapy.[6] Those who underwent vertebral augmentation were 22% less likely (pooled hazard ratio [HR] 0.78, 95% CI 0.66–0.92, p=0.003) to die at up to ten years following treatment than those managed conservatively. Reduced pain, vertebral height loss, and kyphotic deformity resulting in improved mobility and pulmonary function is a likely cause of the decreased mortality after vertebral augmentation.[50,54,55] Interestingly, balloon kyphoplasty demonstrated some benefit over vertebroplasty (HR 0.77, 95% CI 0.77-0.78, P<0.001 versus 0.87, 95% CI 0.87-0.88, P<0.001).[6] This may be associated with greater vertebral body height restoration in kyphoplasty compared to vertebroplasty that has been noted.[56,57]

Complications

With adherence to careful technique and optimal visualization, the risk of morbidity or mortality from vertebral augmentation is low (Box 69.3). For treatment of benign osteoporotic fractures, complication rates are approximately 1%.[31] Not surprisingly, they are higher for inexperienced practitioners or those attempting the procedure without adequate image guidance or cement opacification.[31] Major complications occur in less than 1% of the vertebroplasty RCTs.[58]

Similarly, in FREE, complications referable to kyphoplasty in the 149 patients treated were one soft tissue hematoma and one urinary tract infection.[43] Of note, almost all kyphoplasties performed in FREE were performed under general anesthesia, and in neither cohort were the rates of urinary catheterization reported.

• BOX 69.3 Potential Complications

- Infection (osteomyelitis, epidural abscess)
- Paraspinal hematoma
- Fracture (of rib, pedicle, or vertebral body)
- Failure to improve pain or worsening pain
- Pneumothorax (for thoracic levels)
- Cement leakage
  - Nerve or spinal cord damage resulting in paralysis or bowel/bladder dysfunction
- Pulmonary embolus (secondary to cement or fat emboli)
- Hypotension or depressed myocardial function (secondary to free methyl methacrylate monomer or fat emboli)
- Death from cardiovascular collapse or anaphylaxis to the cement

In our experience, both vertebroplasty and kyphoplasty can be performed with local anesthesia and conscious sedation in most cases, and urinary catheterization is not required.

The risks are greater for malignancy related fractures, with an overall complication rate of 5%–10% reported.[59] In the CAFE trial, of the 70 patients treated with kyphoplasty for malignancy related fractures, the only complications referable to kyphoplasty were one superficial wound infection and one patient with a cement leakage to the adjacent disc who had an adjacent fracture the day after the procedure.[5] There were no serious adverse events that were deemed device related. Notably, kyphoplasty was not performed on those who had a vertebral fracture morphology deemed unsuitable as determined by the treating physician. Thus patients with vertebral plana, comminuted fractures, fractures with posterior wall involvement, or those with epidural involvement, which would incur higher risk, were excluded.

The extraosseous passage of cement is an important complication during vertebral augmentation. For vertebroplasty for osteoporotic fractures, small amounts of cement leakage are very common, with 72% of treated vertebral bodies demonstrating cement leaks on post-procedural CT, with majority discal or into segmental veins; none were into the spinal canal.[40] All patients remained asymptomatic. One patient (1%) had an asymptomatic cement segmental pulmonary embolus.[40] Similarly, high rate of cement leakage was noted on same day CT scans in the VERTOS IV study (91%), of which 39% was in the perivertebral soft tissue and 8% in the spinal canal.[35]

For kyphoplasty, a cavity is created and will fill first, theoretically resulting in a lower rate of cement leakage.[60–63] In FREE, cement extravasation occurred in 27% of treated vertebrae. However, this was assessed with intraoperative fluoroscopy and postoperative radiographs.[43] Most were endplate or discal leakages; there was one foraminal leakage, none were into the spinal canal, and there were no cement embolisms. All patients remained asymptomatic.[43] In a small retrospective series with post-procedural CT, the rate of local leakage of bone cement was 87.5% (21/24) for percutaneous vertebroplasty and 49.2% (29/59) for kyphoplasty.[64]

Cement leaks are also common in pathologic fractures.[59,65,66] A retrospective study of CT-guided vertebroplasty for 331 malignant vertebral lesions revealed a local cement leak in 59 (194 of 331 vertebrae).[67] Although osteolysis of the posterior wall was evident in 49% (162 of 331 vertebrae), only 6% (15 of 331) of leaks were into the spinal canal through the posterior cortex. Pulmonary cement emboli were detected in 1 of 53 (2%) chest radiographs and 10 of 88 (11%) chest CT scans.[67] A large single-center study of 106 patients with multiple myeloma treated with vertebroplasty revealed CT detected cement extravasation in 23% of treated vertebrae, mainly into the perivertebral veins (85%) and epidural veins (9%). Cement emboli were detected in the lungs of five patients (5 %). All the leaks were asymptomatic.[68]

Although most extraosseous cement produces no symptoms or long term morbidity, even small amounts of PMMA adjacent to a nerve root, including cement within the foraminal veins, can produce radicular pain.[59] When radiculopathy is produced by cement leakage, the pain can be treated with nerve root block or systemic steroids. The need for surgical decompression is rare,[30] but may be necessary when there is sufficient foraminal cement to cause frank root compression or when sufficient cement has been placed in the spinal canal to cause cord compression or cauda equina syndrome.[26]

Post-procedure and Follow Up Care

Immediately following the procedure, manual compression was applied over the needle access sites for 5 min to promote clotting and prevent hematoma formation, which might increase post-procedural pain. Transfer to the stretcher using log roll precautions may be performed immediately after the procedure, except in the setting of a vertebral cleft where we keep the patient prone on the fluoroscopy table for 15–20 min. The patient was kept supine and flat in bed for 2 h followed by a further hour with the head of the bed at 30 degrees after the procedure. To alleviate immediate post-procedural pain, the patient may be administered 15–30 mg of IV ketorolac unless renal insufficiency is present. Most patients can be discharged on the same day, although more fragile patients may be observed overnight in the hospital. Assessment of the patient shortly after the procedure commonly reveals improvement in back pain. Often, the patient will discriminate a new procedure-related pain, which is typically treated with non-steroidal anti-inflammatory drugs and should resolve over 24–72 h. In the setting of clinical deterioration suspicious for cement leakage, cross-sectional imaging should be performed.

Post-procedural follow up of the patient is important. The patient should be reviewed in the near term (e.g. three weeks) to assess pain and mobility levels and the need for analgesia. It is important to counsel the patient to report any sudden increase in back pain or new back pain, as it may indicate a new fracture, and imaging should be performed. Notably, up to one-third of patients will suffer a repeat fracture within one to three years, with the greatest risk of steroid-induced osteoporosis.[69,70] Thus, prevention of future fractures is particularly important. While the vast majority of recurrent fractures occur at new levels, there is a small percentage of patients that suffer recurrent fracture at a previously treated level, and may gain pain relief from repeat vertebral augmentation.[71] This is said, caution should be taken when interpreting marrow edema at a previously treated level because, according to one study, normal MRI findings following vertebroplasty include persistent or progressive marrow edema at the treated level in up to one-third of patients and up to six months after the procedure.[72]

Summary and Conclusions

Vertebral augmentation can be effectively utilized in symptomatic osteoporotic vertebral fractures as well as symptomatic fractures or lesions secondary to neoplasia which are refractory to conservative medical therapy. The decision to proceed with vertebral

augmentation is influenced by patient history, physical examination, and laboratory evaluation, including advanced imaging such as MRI or nuclear scintigraphy. Serious complications of vertebral augmentation are low, between 1% and 2%. Four placebo-controlled RCTs have demonstrated mixed results for vertebroplasty. Other retrospective case series and conservative controlled trials have demonstrated positive results, highlighting the importance of patient selection in favoring vertebral augmentation.

Key Points

- Vertebral compression fractures are a common cause of pain and loss of independence in middle-aged and elderly individuals.
- Vertebroplasty and kyphoplasty are minimally invasive, image-guided vertebral augmentation procedures that involve the injection of polymethylmethacrylate (PMMA) into a fractured vertebral body that fails conventional medical therapy. The primary goal of augmentation is pain relief and enhanced functional status, with the secondary goals of vertebral body stabilization in cases of fracture.
- Emerging population level evidence suggests a mortality benefit in patients managed with vertebral augmentation compared to patients undergoing conservative management.
- High-profile randomized controlled trials demonstrated mixed benefits for vertebroplasty compared to sham procedures. However, patient selection criteria are heterogeneous between trials.
- Additional randomized controlled trials of vertebral augmentation versus conservative therapy for both osteoporotic and malignant fractures have demonstrated significant improvements in back pain, reduction in disability, and improvement in quality of life in favor of vertebral augmentation.
- Complications are rare and generally result from unrecognized extraosseous leakage of the injected PMMA. These include radiculopathy, paralysis, and pulmonary embolism. These risks can be minimized, and vertebral augmentation can be safely performed by experienced operators using high-quality imaging, preferably with biplane fluoroscopy.

Suggested Readings

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Biopsychosocial Pre-screening for Spinal Cord and Peripheral Nerve Stimulation Devices

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Overview

Pain is a complex and serious medical condition, with estimates from the Centers for Disease Control and Prevention in 2016 showing 50 million (20.4%) United States adults experiencing chronic pain, among whom 19.6 million experience high impact pain that limits life or work activities.[1] Beyond the element of human suffering, there are enormous economic costs associated with chronic pain in terms of lost productivity and medical care. Among individuals who continue to work, common pain conditions alone (back pain, headache, arthritis, and musculoskeletal pain) may account for up to $61 billion in lost productivity annually in the United States alone.[2] According to statistics from the Institute of Medicine (2011), the societal cost of all chronic pain and related disability in the United States is $560–635 billion each year.[3] Gaskin and Richard[4] note that these annual costs for pain were greater than the annual costs for heart disease, cancer, and diabetes. The Institute of Medicine Report, "*Relieving Pain in America*"[3] has highlighted the urgent need to develop more cost effective approaches to pain management because the ever-increasing costs associated with current treatment approaches cannot be sustained. In parallel with trends showing increasing chronic pain, there has been considerable concern regarding the use of opioids to treat chronic pain, given their widespread use and potentially lethal side effects.[5] Therefore there is still an urgent need to develop opioid-sparing and cost effective methods for managing chronic pain, especially when it becomes intractable.

Over the past two decades, there has been an expanding role for neuromodulation procedures such as spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS) as treatment options for intractable chronic pain. Traditional neuromodulation has been presumptively operated by Melzack and Wall's[6] *gate control theory of pain*, which proposes that the activation of low-threshold afferent nerve fibers decreases the response of dorsal horn neurons to unmyelinated nociceptors, thereby "closing the gate" to pain transmission from the spinal cord. Shealy, Mortimer and Rewick[7] were the first to apply this when they stimulated the dorsal columns to treat chronic, intractable cancer pain. Since that time, level 1 evidence has accumulated in support of implantable dorsal column stimulation to treat axial back pain, lumbar radiculopathy or neuralgia, and complex regional pain syndrome.[8] Proposed mechanisms for SCS depend on the modality but have included action at the dorsal column,[9] dorsal horn,[10] dorsal root ganglion,[11] and supraspinal sites.[12,13]

Neuromodulation of targets not amenable to neuraxial stimulation has focused on the use of semi-permanent and implantable PNS with a history nearly as long as that of dorsal column stimulation.[14,15] Nerve regions that are more easily accessed by PNS include the trigeminal nerve, occipital nerve, and subcutaneous peripheral nerves. Conditions for which PNS may be indicated include trigeminal neuropathic pain,[16] occipital neuralgia,[17] supraorbital neuralgia, residual limb, and phantom limb pain,[18] and inguinal neuralgia (although emerging technologies such as dorsal root ganglion stimulation may be appropriate for inguinal chronic post-surgical pain). Headache disorders, including migraines and cluster headaches, might also benefit from cranial forms of PNS.[19,20]

Successful results with SCS and PNS have been defined variously in clinical trials. Some investigators and practice guidelines identified greater than 50% relief of pain 12-months following implantation as a potential benchmark.[21,22] Although success rates vary widely from 40%–80%, conditions commonly treated by SCS include failed back surgery syndrome, painful peripheral vascular disease, neuropathic pain, multiple sclerosis (MS), and complex regional pain syndrome (CRPS, previously known as reflex sympathetic dystrophy).[23–29] The initial expense of these implantable therapies has been shown to be potentially offset in the long term by the benefits and resultant reduction in treatment expenses. Early work by Kumar, Malik, and Demeria evaluated costs for patients who received SCS and compared them to the costs for treatment by conventional pain therapies (CPT).[26] While the cost for SCS was significantly higher than for CPT in the first 2.5 years, after that time the cost of treating patients with SCS not only became less than the cost for CPT, but it also remained less expensive during the remainder of the five-year follow up period.[26] Another analysis of SCS compared to conventional therapies has found SCS to potentially create cost and healthcare resource utilization savings, though perhaps at the risk of higher complication rates.[30]

Adverse events associated with spinal cord stimulators have been several, as have reasons for SCS therapeutic failure because of ineffective pain relief. Adverse events are typically separated into

either mechanical (e.g. lead migration, lead or implanted pulse generator failure, lead fracture) or biologic problems (e.g. surgical site infection or loss of efficacy). The incidence of complications of any type varies from 30%–40% in contemporary series.[31] The rate of explant for any reason has been shown to be approximately 8% per year in a large European multicenter cohort study.[32] The study consisted primarily of patients with post-laminectomy syndrome, approximately half of these devices were removed because of inadequate pain relief.[32] In a multicenter retrospective United States based study of SCS explant primarily among patients treated with SCS for post-laminectomy syndrome, Pope and colleagues found that the most common reasons for device explant consisted of loss of efficacy (43.9% of explanted devices) followed by mechanical complications or infection (20.2%).[33] These findings, among others, highlight the need for patient selection to hopefully reduce the rate of explanation for lost efficacy.

Efforts to improve patient selection for the surgical treatment of back pain, including post-laminectomy pain treatment with SCS, have a five-decade history. In an attempt to determine both the positive and negative outcome indicators for surgical procedures, Spengler and Freeman[34] initially performed a retrospective analysis of 30 patients who had unsuccessful outcomes from various surgical procedures for either low back pain or sciatica or both. Among their findings, the most commonly reported cause of the poor results was a poor initial candidate-selection process, despite indications for the surgical procedures. A more focused investigation identified instances of drug abuse, alcoholism, marital discord, and personality factors that were felt to have played a role in the patients' post-surgical success or failure. Therefore Spengler and colleagues[34] recommended pre-surgical psychological evaluation in order to reduce the likelihood of unsuccessful procedures. Following these reports, Long and colleagues[35] performed a retrospective analysis of their own patients, who received surgically-implanted dorsal column SCS between 1970 and 1973. At that time, the only method for identifying candidates for this procedure was continued self-report of pain after failing all other treatments. They found that only 33% of patients (12 of 36) achieved adequate pain relief over the seven-year follow up. Approximately one-half of those patients originally selected for the procedure would have been rejected using updated inclusion criteria for psychosocial factors, including substance use disorders.

Given the substantial burden of chronic pain, the numerous indications for neuromodulation therapy, high initial costs for implantation of neuromodulation systems, and the relatively high rate of explantation for loss of efficacy, there is a substantial value for improved patient selection before use of this therapy. This chapter will review the tools that have been developed to facilitate patient selection for surgical treatment of spinal pathology and its pain-related conditions treated with SCS. Specific attention will be devoted to initial research on patient selection for spine surgery, followed by the extension of these approaches to SCS. Before reviewing current research on this topic, a discussion of the biopsychosocial approach to assessment is warranted.

The Biopsychosocial Approach to Assessment

The biopsychosocial approach is recognized as the most comprehensive and heuristic approach to the evaluation of medical disorders.[36–40] The biopsychosocial model focuses on the complex interaction among biologic, psychologic, and medicolegal variables that patients encounter when coping with a persistent, distressing medical condition such as chronic pain. A range of psychological, social, and economic factors interact with the physical pathology to modulate a patient's discomfort and disability associated with the condition. This complex interaction accounts for the likelihood that a patient's life will be adversely affected in various ways by his or her medical condition, thus requiring a comprehensive assessment and treatment approach designed to address the biologic, psychological, and social aspects of care. This approach contrasts with the traditional biomedical reductionist approach, which assumes that most medical conditions, including chronic pain, can be separated into distinct, independent physical and psychosocial components.

A demonstration of this model and highlights how individuals significantly differ in the frequency of reporting physical symptoms, tendency to visit physicians when experiencing identical symptoms, and in their responses to the same treatment.[41] These, in turn, are not fully predicted by the physical findings. A comprehensive assessment of a patient proceeds from a global biopsychosocial diagnosis of the disorder in question to a more detailed evaluation of the most important interactive factors needed for the diagnosis.[37,38] For example, for a patient reporting low back pain, a comprehensive physical examination would initially be conducted to assess the bio-component of the equation. However, this becomes less valuable when it is non-specific or demonstrates pain inhibition, leading one to question the contribution from other elements in the biopsychosocial model. As such, contemporary models of treatment, particularly for back pain, now recognize that psychological and social influences may contribute substantially to symptoms, disability, and response to treatment.[42]

Thus, a comprehensive biopsychosocial assessment of each patient is needed before the development of a treatment plan. Current surgical risk assessment techniques for spine surgery and neuromodulation seek to account for both medical risk factors as well as the psychosocial attributes that may predict the likelihood of a successful outcome or, as it is often framed in the literature, association with a poorer outcome. Therefore any successful assessment of patients will need to evaluate these various factors comprehensively. The following discussion will focus primarily on the psychosocial evaluation for this process.

The Biopsychosocial Pre-screening Process

Clinical Framework for Biopsychosocial Pre-screening

The process of test selection for biopsychosocial pre-screening can be difficult for the clinician not experienced with this process, given the number of available instruments in the literature. A complete review of all these instruments is beyond the scope of this text. However, Block and colleagues have carried out foundational research in this area, and their work will be used as a frame for this discussion. They have broadly classified the psychosocial factors associated with poor surgical outcomes in the back pain patient as[43]: personality and emotional factors, cognitive-behavioral factors, and environmental factors. They also noted medical risk factors associated with poorer outcomes, including increased duration of pain, number of previous surgery for the same problem, invasiveness of the surgery, and smoking.[36,43–45] These can be used as a starting point for the clinician who has been asked to screen and evaluate patient candidates for SCS or PNS.

Intake Survey

A general survey of pain symptoms is a necessary starting point for any pretreatment evaluation in a pain program. Assessment should include a thorough history of the pain syndrome, including the date of onset and pertinent details of the pain condition as well as prior treatments or surgeries. Clinical factors that have been associated with positive outcomes with SCS for back pain include predominant neuropathic leg pain, SCS within three years of first back surgery, and absence of psychological risk factors.[46,47] Environmental, historical, and medical factors are also assessed during intake by investigating self-report items such as demographic information, employment status, education level, disability payment status, workers' compensation or personal injury litigation involvement, healthcare utilization, marital status, family support network, and other comorbid chronic health problems (i.e. smoking and obesity), all of which have been identified as potential predictors of worse outcomes with SCS.[44,48]

In addition to the general intake assessment, individual tools may be used to assess each of the domains identified by Block and colleagues.[44]

General Assessment: Pain Intensity, Disability, and Medication Use

First developed in 1976, the *Visual Analog Scale* (VAS), also referred to as the *Pain Drawing Analog* (PDA),[49] is a scale designed to rate the patient's degree of pain on a scale from zero (no pain) to ten (worst possible pain). Comprised of a 10 cm horizontal line divided at two-point intervals, patients mark an "X" on the line to represent current levels of pain. The psychometric properties and utility with chronic pain populations of the VAS/PDA are further described in the literature.[50,51]

A further development of the VAS/PDA is the *Million Visual Analog Scale* (MVAS).[52] The MVAS consists of 15 self-report items specific to perceived pain and disability. Patients respond on a 10 cm line, representing a range of possible answers from zero to ten, in which the total score is the sum of all responses. Various cutoff points have been described based upon psychometric testing of the MVAS. Scores of 0–39 indicate "mildly disabling" pain; 40–84 indicate "moderately disabling pain"; and 85 and above indicate "severely disabling pain." The MVAS is especially helpful for discrepancies, such as when self-reported pain is higher than expected based on physical findings. This is often suggestive of a potential psychosocial component in the patient's experience of pain.[53] Newer measures of global pain and multidimensional factors contributing to pain have been derived from national item data banks and include the Patient Reported Outcome Measure Information System (PROMIS 29).[54] This measure has been updated over time and is now in a second version,[55] and has been shown to adequately predict disability score (i.e. Oswestry Disability Questionnaire score) among patients presenting for lumbar spine surgery.[56]

The *Oswestry Disability Questionnaire* is a self-report scale designed to assess the degree of functional impairment because of the pain condition.[57] Consisting of ten items regarding limitations of activities of daily living because of pain, the Oswestry has demonstrated test-retest reliability of 0.99 with a 24 h interval between administrations, as well as acceptable levels of validity.[58,59] Each item is scored on a zero-to-five-point scale, with a potential range of scores from zero to 50, with higher scores significant for higher levels of pain-related limitations.

Adams and colleagues[60] developed the *Pain Medication Questionnaire* (PMQ) to determine the risk of medication misuse among chronic pain patients. Identified behavioral correlates and attitudes suggestive of medication misuse were used to develop the 26 self-report items that make up the PMQ. Higher scores indicate a greater likelihood of substance abuse potential, emotional distress, impaired coping skills, reduced physical functioning, as well as higher rates of unemployment.[60]

Additional tools designed to specifically assess the risk of mediation misuse and monitoring for adverse effects, specifically for opioids, include the Screener and Opioid Assessment for Pain Patients (SOAPP-R),[61] and the Current Opioid Misuse Measure.[62]

Emotional Factors: Assessment of Mood

Mood factors have been implicated widely in the patient experience of chronic pain, and pre-implant levels of distress, including depression and anxiety, have been associated with a lower level of pain reduction among patients receiving SCS implants.[48]

The *Beck Depression Inventory* (BDI-II) is a 21-item self-report inventory designed to assess the intensity of depressive symptomatology.[63] Each item is scored from zero to three, with a potential range of scores from zero to 63. A total score of zero to nine is considered normal, 10–15 is mild depression, 16–19 represents mild to moderate depression, 20–29 reflects moderate to severe depression, and 30+ indicates severe depression. Being able to identify symptoms of depression is important in chronic pain populations, as is being able to delineate between cognitive and somatic specific symptoms, which is an option allowed by the BDI-2. To obtain more than the subjective self-reported symptoms of depression available with the BDI-2, an experienced clinician will also want to perform a more objective assessment of depression to validate or clarify their findings. One tool that is widely available, but does require some training and experience, is the *Hamilton Rating Scale for Depression* (HAM-D),[64] which is administered by the clinician in a brief interview format and could potentially be incorporated into the overall clinical interview.

Anxiety has typically been measured using the *Hospital Anxiety and Depression Scale* (HADS),[65] which can be particularly useful for its separate anxiety and depression subscales as well as an additional option for measurement of depression.

Personality Factors

In addition to examining the current emotional status of the patient candidate prior to SCS or PNS implantation, long-standing personality traits are important to consider before a patient begins the life-changing process that implantable therapies entail. In general, neuroticism has been shown to be one of the most predictive personality factors determining the outcomes of pain-related treatments,[66] and has also been shown to be the personality psychopathology factor most strongly associated with negative outcomes among patients receiving SCS.[67]

Although personality inventories can be lengthy and time consuming, they have been used extensively in chronic pain populations. Third-party payers may limit the type or extent of testing that is performed with pre-surgical candidates; two inventories reviewed next provide valuable insight into the characteristic way these patients relate to the people and situations around them. If time and the situation allow, they should be considered part of the comprehensive pre-screening evaluation prior to SCS implantation.

The *Millon Behavioral Medicine Diagnostic* (MBMD) is a 165-item, self-report inventory that examines psychosocial factors that may impact treatment outcomes with medical patients.[68] The MBMD includes 29 clinical scales, three response pattern scales, one validity indicator, and six negative health habits indicators.

It is intended for adult clinical and rehabilitation patients (aged 18–85 years) who are undergoing medical care or surgical evaluation, making this a valuable resource for the pre-screening process.

A more widely recognized personality assessment that has been used extensively in chronic pain research, including that conducted by Block and colleagues, is the *Minnesota Multiphasic Personality Inventory-2* (MMPI-2).[69] The MMPI-2 is a 567-item, self-report measure of personality functioning and psychiatric symptoms. It is the most commonly used personality assessment for patients with chronic pain, who often demonstrate a higher prevalence of emotional distress, specifically depressive symptoms and potential personality disorders, relative to the general population.[70] There are ten empirically derived clinical scales, various supplementary scales, and validity scales provided to assess the test-taking attitudes of the patient. The MMPI-2 has great utility when used as part of the pre-screening process with chronic pain patients. Findings from the MMPI-2 can help in the identification of psychopathology, personality, and behavioral characteristics, treatment planning, and prediction of treatment outcomes.[70] However, one must keep in mind that the use of this test in chronic pain patients may present challenges because of the physical symptoms reported in this population.[71]

A revised form of the MMPI-2, the MMPI-2 Restructured Form (MMPI-2-RF)[72] has been used in more recent work by investigators.[73] Profiles obtained with this instrument have been shown to be approximately similar between cohorts of patient candidates for spine surgery and SCS implantation.[74] These profiles have also been associated with surgical outcomes, including pain level, Oswestry Disability Index, and work status following surgery.[75] Similar findings have been demonstrated in patients undergoing SCS implant, with poorer outcomes observed among patients with higher pre-implant MMPI-2-RF scores on scales that assess emotional dysfunction, somatic/cognitive complaints, and interpersonal problems.[67]

Cognitive and Behavioral Assessment

The clinician performing the pre-screening must identify the coping skills that patients already rely upon, as these will likely be the same skills employed during the trialing and post-implant phase of treatment. If there is a notable lack of healthy coping skills, this is something that might be managed prior to, and following, surgery with biobehavioral therapy.[76]

Pain-related beliefs also play an important role in functional recovery after SCS implant. Catastrophizing as a construct includes thought patterns of magnification of pain-related symptoms, rumination on pain, feelings of helplessness, and pessimism about expected outcomes. Greater degrees of catastrophizing are a strong predictor of negative outcomes for continued disability following spine surgery[77] and SCS implantation.[78] The degree of catastrophizing can be measured using the *Physical Component Scale* (PCS),[79] which is a well-validated self-report tool for catastrophic thinking related to pain.

The *Coping Strategy Questionnaire* (CSQ)[80] is a 42-item self-report inventory that assesses how often pain patients use six cognitive coping strategies and two behavioral coping strategies. These strategies include diverting attention or distraction, reinterpreting pain sensations, ignoring pain, praying and hoping, coping self-statements, increasing behavioral activities, and catastrophizing. Additionally, the CSQ measures the subjective ability to control and decrease pain. Patients rate some activities, in relation to pain, on a six-point scale: 0 = never do that, 3 = sometimes do that, and 6 = always do that.

Current quality of life is also an important factor for patients being considered for an implantable therapy device, as undergoing SCS implantation can interrupt current lifestyle during trialing, implantation, and surgical recovery. The *Medical Outcomes Survey 36-Item Short-Form Health Survey* (SF-36)[81] is a 36-item questionnaire that assesses health related quality of life, both physical and mental, from the patient's perspective. The SF-36, and variants of this measure, is widely used for assessment and follow up monitoring of healthcare treatment outcomes. The SF-36 consists of eight subscales and two standardized summary scales, the Mental Component Scale (MCS) and the Physical Component Scale (PCS). The MCS and PCS provide an overall gauge of the patient's sense of physical and mental well-being.

While these assessment tools are useful in performing a comprehensive pre-screening evaluation, it is up to the clinician to obtain the proper training to perform these assessments, along with a thorough clinical interview. These data can then be used to prepare a detailed report of their findings for the patient and physician performing the implantation procedure. In addition to performing these tasks, it should also be within the clinician's repertoire to know how to ask the following: what treatments the patient has found helpful in the past; what prescriptions and over-the-counter medications they are taking; what their activities of daily living entail now and prior to their pain condition; and what their realistic expectations are for life post-procedure.

Foundational Work on the Pre-screening Process for Spine Surgery

Initial work on pre-screening of patients who were being considered for spine surgery occurred throughout the 1970's–1990's.[44,45,82,83] Epker and Block[44] reviewed the methods for predicting positive outcomes for spine surgery in general and highlighted the positive and negative psychosocial risk factors that appeared to impact recovery from spine surgery. They delineated specific risk factors predictive of poor surgical outcomes and suggested the evaluation and quantification of these factors before performing spine surgery. Three major categories of psychosocial factors were described, as noted previously: 1) personality/emotional, 2) cognitive/behavioral, and 3) environmental/historical. Scale elevations on the MMPI-2 associated with pain sensitivity (Scales 1 and 3), depression (Scale 2), anger (Scale 4), and anxiety (Scale 7) were found to be associated with negative outcomes. Other significant factors included maladaptive coping strategies, workers' compensation status, litigation related to pain, and drug and alcohol abuse. Epker and Block also discussed "quasi-medical" risk factors that could predict poor results: the duration of pain and number of previous surgeries for pain are negatively correlated with positive outcomes, and smoking and obesity can also negatively affect recovery from surgery. Finally, they note that the presence of non-organic Waddell signs can help identify those candidates who will have poor outcomes.[84]

Subsequently, a comprehensive screening approach for spine surgery was presented by Block et al.[36] They developed a "scorecard" to clarify the spine surgery candidate's biopsychosocial risk factors, using various factors. The scorecard lists and quantifies psychosocial risk factors, along with additional medical risk factors. Based on the existing research demonstrating predictive ability, each risk factor is assigned an *a priori* weight of high risk,[2] or medium risk,[1] and the risk factors in each group (medical and psychosocial risks) are then totaled to arrive at a surgical prognosis.[45] In that study, 204 patients were referred for psychosocial screening and were evaluated no more than one month prior to surgery.

A semi-structured interview and two psychosocial questionnaires, the MMPI-2 and the Coping Strategy Questionnaire (CSQ), were used to evaluate the psychosocial and medical risk factors. Based on the results of screening, patients were placed into one of three predictive categories ("good", "fair", or "poor"). Analyses of results showed the screening achieved an 82% accuracy rate, with 82.3% patients in the "good group" experiencing a good outcome and 83.0% patients in the poor prognostic group resulting in poor outcome.[45] Logistic regression analyses were also conducted to determine which variables were the most significant predictors of outcome. These analyses yielded psychosocial test data as the most significant cluster of variables to correctly classify patients, with a correct classification rate of 78.4%. The addition of psychosocial interview data brought the model up to an 83.3% correct classification rate. Finally, the addition of the medical risk factors contributed slightly, bringing the total model to 84.3% correctly classified. This study was the first empirical investigation to show that many psychosocial and medical risk factors can be identified, quantified, and used to accurately predict surgical outcomes.[45]

The original screening "scorecard"[45] was subsequently replaced with a new prognostic algorithm by Block et al. in 2001.[36] This algorithm added several new features that enhanced its predictive utility:

- The algorithm placed psychosocial risk factors above all others because it has the most predictive power.
- A category termed "adverse clinical features" was also included to account for factors such as inconsistency, compliance issues, and medication seeking (that were often found in the patients' medical charts and observed during the clinical interview).
- A set of general treatment recommendations was added. The psychologists' recommendations can fall into several categories: 1) proceed with surgery; 2) surgery, but with postoperative psychosocial treatment sessions; 3) preoperative treatment psychosocial sessions prior to surgery; 4) only non-invasive therapy recommended.

This scorecard and screening algorithm were again updated in 2019 to account for the restructured form of the MMPI-2-RF.[73]

Advancement of Pre-screening Research and Use for SCS

Prior to the work by Block and colleagues examining the role of psychosocial risk factors in spine surgery, there were few studies that had systematically evaluated the predictive value of biopsychosocial risk factors and treatment outcomes for implantable SCS devices.[85–87]

Studies by Schocket et al.[88] and Heckler and colleagues[89] examined whether the screening algorithm used by Block for spine surgery pre-screening could predict outcomes in SCS or intrathecal medication therapy for back pain. These studies assume that psychological variables are broadly predictive of patient psychological resilience and response to the stresses of surgery. Their screening algorithm used a combination of clinical interviews, psychosocial testing (BDI, MCS, HAM-D, CSQ), and other psychosocial and medical risk factors (Table 70.1). One significant difference in their work compared with that by Block and colleagues was the decision to forego extensive personality testing with the MMPI-2 and instead rely upon other measures of mood and coping. Based on this algorithm, patients were classified into one of five groups: Green (proceed with surgery); Yellow I (proceed with surgery but administer postoperative psychosocial intervention); Yellow II (administer preoperative psychosocial intervention before surgery); Red (only non-invasive intervention is recommended). Data were collected from patients who were able to complete six- and 12-month follow up evaluations. The Green group showed 40% of patients to be taking no new medications at the six-month follow up. This percentage decreased as prognosis worsened (Yellow I, 27.3%; Yellow II, 25%; and Red I and II, 0%). When the Green group was compared to the Red group, significantly better outcomes were observed with respect to pain scores, disability measures, depression, and mental and physical status.

TABLE 70.1 The Psychosocial and Medical Risk Factors Used by Schocket (89) and Heckler (90)

Psychosocial Risk Factors
• Job Dissatisfaction
• Workers' Compensation Status
• Pending Litigation
• Spousal Solicitousness or Lack of Support
• Abuse and/or Abandonment History
• Substance Abuse
• History of Psychosocial Disturbance
• Pain Sensitivity
• Chronic and/or Reactive Depression
• Pathological Depression Profile
• Anger
• Anxiety
Medical Risk Factors
• Longer Duration of Pain
• Type of Surgery
• Presence of Non-organic Signs
• Abnormal Pain Drawing
• Previous Surgeries
• Prior Medical Problems
• Smoking Status
• Obesity

Subsequent studies in this line of the literature have contributed further insight into factors that may be associated with poor outcomes following SCS implantation. The addition of testing for mechanical allodynia using Quantitative Sensory Testing was shown to predict outcomes among patients with CRPS type 1 treated with SCS.[90,91] Additional work on the use of MMPI-2-RF for surgical outcome risk stratification suggested a similar predictive value for this test in both spine surgery and SCS implant populations,[74] thus suggesting that the risk factors and expected outcome findings in their work with spine surgery patients may generalize to patients referred or SCS implant. In a retrospective study,[92] the authors divided patients into those who maintained 50% pain relief at one-year follow up after SCS implant for various conditions (49% had post-laminectomy syndrome) and those who did not achieve pain relief. They found that pre-implant low scores for sleep interference, depression, catastrophizing, and low self-efficacy were associated with less than 50% pain relief at the one-year follow up. Although they noted that sleep interference seemed to be the strongest predictor, this was not measured using a validated questionnaire and therefore may have been a confounder in multivariate analysis.

Further evidence in a large, retrospective post-market survey of patients with SCS found that patients with a pre-implant PCS score of greater than 30 were associated with a five times greater risk of dissatisfaction with the SCS device and a three times greater risk of reporting poor quality of life at six- and 12-months post-implant.[93] In another small study,[78] the authors found that predictors for a patient receiving SCS implant to receive a meaningful clinical improvement in pain and health related quality of life

• BOX 70.1 Factors Associated With Failure or Success of SCS

Failure

- Unfavorable pre-implant scores in sleep interference, depression, catastrophizing, self-efficacy*
- Pain Catastrophizing Scale score greater than 30**
- Benzodiazepine use
- Depression and anxiety
- Low scores on patient activation (obtaining information, decision making, and resilience)

Success

- Greater than 80% coverage of the painful area
- Lower levels of anxiety and catastrophizing symptoms
- Shorter pain duration
- Female gender
- No opioid use

*Associated with less than 50% relief at one-year follow up
**Associated with five-time greater risk of dissatisfaction with SCS and three times greater risk of poor quality of life at six and 12 months after implant

included greater than 80% paresthesia coverage of the painful area, lower levels of anxiety, and catastrophizing symptoms, shorter pain duration, female gender, and no use of opioids before surgery. Other investigators found benzodiazepine use to be a predictor of poorer outcomes in patients with SCS.[94] Although the authors used chart review for measurement of coincident mood disorders. There is also evidence of a high prevalence of undiagnosed depression and anxiety in this population, confounding this association.[95] Investigation into mood disorders with SCS removal has shown that patients having explant display high rates of depression (64%) and anxiety (35%).[96]

Block and colleagues[97] published the most recent evidence for a novel predictor for poor outcomes in SCS. Their group, as well as other authors, have proposed that the construct of patient activation may mediate many of the identified risk factors for poor outcomes after SCS implantation.[98] Of particular interest is the finding that even among patients with known psychological risk factors for poor outcomes, higher scores on patient activation (i.e. involvement in obtaining information, decision making, and resilience) may substantially reduce the risks from these attributes. The factors that contribute to the failure or success of SCS are listed in Box 70.1.

In summary, the studies by Schocket[88] and Heckler[89] continue to provide robust models for a pre-screening algorithm prior to SCS implant. Subsequent investigations have identified additional potential risk factors, and there is a clear opportunity for an updated algorithm incorporating these supplementary insights for SCS and PNS patient pre-screening.

Future Directions for Patient Screening

Future directions in the area of patient screening prior to SCS and PNS implantation will continue to focus on expanding the validity and generalizability of models (described above). Additionally, tools to assess and monitor patients with chronic pain prior to SCS implantation will be more time efficient for both patients and personnel, more cost effective for systems and payers, and increasingly automated. Emerging technologies have shown promise for the characterization of pain states, facilitation of diagnosis,[99] and patient monitoring during trial for an implanted device.[100] In addition to instruments used in the research setting, guidelines are beginning to incorporate online patient pre-screening tools for SCS. A clinical guideline by a multi-disciplinary European panel on referral and selection of patients for spinal cord stimulation includes a web-based tool on medical and psychosocial factors on which SCS is likely to improve the patient's pain syndrome. This tool is freely available at https://www.scstool.org/.

Summary and Conclusions

When pain becomes intractable in nature, invasive pain control interventions may provide pain relief. Neuromodulation therapies such as spinal cord and PNS have strong evidence supporting their efficacy among select patient populations. However, surveillance data reveal that therapeutic failure because of loss of efficacy for pain control is challenging, highlighting the need for continued vigilance during patient pre-screening prior to device implantation. The body of work strongly suggests that psychological and/or social factors are important determinants of neuromodulation treatment outcomes for SCS and PNS. A comprehensive biopsychosocial evaluation and a suitable recommendation by a trained healthcare professional, such as a psychologist, is the minimum standard of practice and the best practice for patient evaluation prior to making the decision on neuromodulation. Similar recommendations have been found in bariatric and transplantation surgery. Familiarity with these assessment instruments is essential for any pain clinician considering the use of neuromodulation therapies.

Substantial progress has been made in identifying risk factors for poor outcomes after neuromodulation. These findings are being incorporated into clinical algorithms should they continue to show validity in the research setting. Given the substantial societal costs of chronic pain, there is great interest in the use of these technologies for the treatment of pain. However, cost effectiveness research has highlighted the need for several years of efficacious therapy for the value of these devices to be realized. In addition to the necessity for biopsychosocial evaluations in making the decision to proceed with neuromodulation, there is a strong argument to be made as well in favor of continued development of pre-screening tools that allow us to maximize the benefits of this technology and deploy it in a cost effective manner.

Key Points

- Use of neuromodulation technologies, SCS and PNS, for the treatment of chronic pain presents a strong value proposition. However, for value to be realized, these therapies require careful patient selection to avoid premature explantation of the device because of loss of efficacy.
- The biopsychosocial (BPS) model focuses on the complex interaction among biologic, psychological, and medicolegal variables that accounts for the likelihood a patient's life will be adversely affected in a variety of ways by his medical condition, thus requiring a comprehensive assessment and treatment

approach designed to address all aspects of required care (i.e. biologic and psychosocial).
- Employment of the biopsychosocial model in the clinical setting has resulted in more effective pre-screening of patients for spine surgery, and these instruments and methods are being utilized for patient pre-screening prior to neuromodulation device implantation.
- The major categories of psychosocial factors that negatively influence outcomes in spine surgery and SCS implantation to include 1) personality/emotional, 2) cognitive/behavioral, and 3) environmental/historical.
- A comprehensive biopsychosocial evaluation by a trained professional, such as a psychologist, with a recommendation to proceed, is a necessity for neuromodulation therapy.
- Investigators initially developed a screening algorithm for patients being considered for spine surgery. This modified pre-screening protocol was later modified for patients being considered for implantable devices.
- Based on prognostic algorithms for SCS implantation, a patient's suitability as candidates are classified into the following categories: Green (proceed with surgery); Yellow I (proceed with surgery but administer post-operative psychosocial intervention); Yellow II (administer pre-operative psychosocial intervention before surgery); Red (only non-surgical intervention is recommended).
- Additional clinical research is needed to refine the screening techniques and examine their predictive utility for long term outcomes.

Suggested Readings

Block AR, Ohnmeiss DO, Guyer RD, Rashbaum RF, Hochschuler SH. The use of presurgical psychological screening to predict the outcome of spine surgery. *Spine J.* 2001;1(4):274–282.

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Spinal Cord Stimulation, Peripheral Nerve Stimulation, Restorative Neurostimulation, Deep Brain Stimulation, and Motor Cortex Stimulation

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Introduction

Neuromodulation for chronic pain control has been used for several decades but recently has received much clinical interest mainly based on published improved therapy outcomes.[1] Spinal cord (SCS), dorsal root ganglion (DRG), and peripheral nerve stimulation (PNS) for chronic pain are the mainstay of neuromodulation therapies and will be the focus of this brief review. Over the last 30 years, traditional, low frequency, paresthesia-based (40–90 Hz) SCS stimulation has been used. However, only approximately 30%–50% of patients received more than 50% of pain relief when conventional low frequency SCS therapy was used.[2,3] Recently discovered SCS therapies, such as continuous stimulation at a higher frequency (10 kHz), DRG stimulation, closed-loop SCS, or differential target multiplex types of SCS, were found to be superior to traditional SCS when used for chronic severe back and leg pain.[4–8] Prior studies also showed an additional benefit when traditional low frequency SCS was modified into 1 kHz continuous SCS,[9,10] or 500 Hz burst pattern[11] of stimulation.

SCS Mechanisms of Action

Initial studies utilizing traditional low frequency SCS suggested activation of the gate control mechanisms, blockade of pain conduction via the spinothalamic tract, supraspinal sympathetic suppression mechanisms, and activation or release of the neuromodulators as major mechanisms of pain control.[12] When SCS is active, unmyelinated afferent fibers (A δ and C) are inhibited by the electrical stimulation of non-nociceptive, myelinated afferent fibers. Blockade of supraspinal sympathetic mechanisms by SCS results in an increase in peripheral blood flow with transitory inhibition of sympathetic vasoconstriction.[13] Activation or release of various neuromodulators such as σ-aminobutyric acid (GABA) in the dorsal horn,[14,15] glycine release in the extracellular space of the spinal cord, and inhibition of glutamate and aspartate release in the dorsal horn contribute to SCS, resulting in chronic pain relief.[16]

SCS affects heart function by reducing the intrinsic cardiac nervous system activity,[17] preemptive suppression of marked increase in sympathetic outflow,[18] which may then inhibit local heart circuits and decrease the frequency of arrhythmias in ischemic hearts.[19] SCS does not affect coronary blood flow during ischemic conditions, and there is no effect on left ventricular function or left ventricular blood flow distribution.[19,20] However, the positive and anti-ischemic effects of SCS include decreased oxygen demand, a significant increase in cardiac pacing tolerance, decreased ST segment depression, and improved myocardial lactate metabolism, which in turn results in an improvement in exercise tolerance and pain relief.[21]

SCS improves ischemic pain in the extremities by a vasodilator effect via calcitonin gene-related peptide (CGRP), peripheral prostacyclin release,[22] and profound neuronal increase of nitric oxide.[23] During SCS, there is a decreased sensitivity to vasoconstrictive sympathetic stimuli,[24,25] and an increase in skin blood flow measured by transcutaneous partial oxygen pressure and increased pulse-wave amplitude.[26]

Other mechanisms of SCS include a significant modulatory effect on dorsal horn pain pathways (in addition to dorsal columns) with the recruitment of inhibitory neurons when SCS is used at 10 kHz [27]. Such effects result in additional pain relief, not exhibited greatly when low frequencies (1–1200 Hz) of SCS were used.[27]

Recently, attention has been directed at the effect of SCS on glial cells, in addition to neurons. Glial cells respond to electrical field applications by depolarizing, releasing neurotransmitters, and communicating with each other. The differential target multiplex (DTM) type of SCS is directed toward the modulation of glial cell response. In an acute neuropathic pain model in rodents and mammals, the DTM type of SCS provided superior thermal and mechanical hypersensitivity suppression than low and high (1000 Hz) frequency SCS.[28] During DTM SCS in an animal model of neuropathic pain, gene expression is better restored toward the baseline, non-pain state, when compared to low and 1000 Hz frequency SCS,[29] including those genes related to neuroinflammation.[30]

Finally, a recent development in SCS waveform optimization is a closed-loop stimulation. During closed-loop stimulation, data regarding the spinal cord response to stimulation, measured as evoked compound action potentials (ECAPs), were recorded in real-time. This allows the spinal cord stimulator system to adjust its stimulation parameters to maintain an ideal therapeutic response.[31]

Dorsal root ganglia stimulation (DRG) acts directly on the development of neuropathic pain through inhibition of hyperexcitability and the spontaneous, ectopic firing of neuronal cell bodies contained within the DRG. These processes are known to contribute to central sensitization and clinical allodynia. DRG electrical stimulation reduces the propagation of action potentials to the dorsal horn, affects the release of neuromodulators in the dorsal horn aimed at decreasing excitability and excess neuronal firing and possibly deactivation of hyperexcitability of dorsal horn wide-dynamic range neurons, and an increase in membrane firing thresholds.[32,33]

Spinal Cord Stimulator Trial Technique

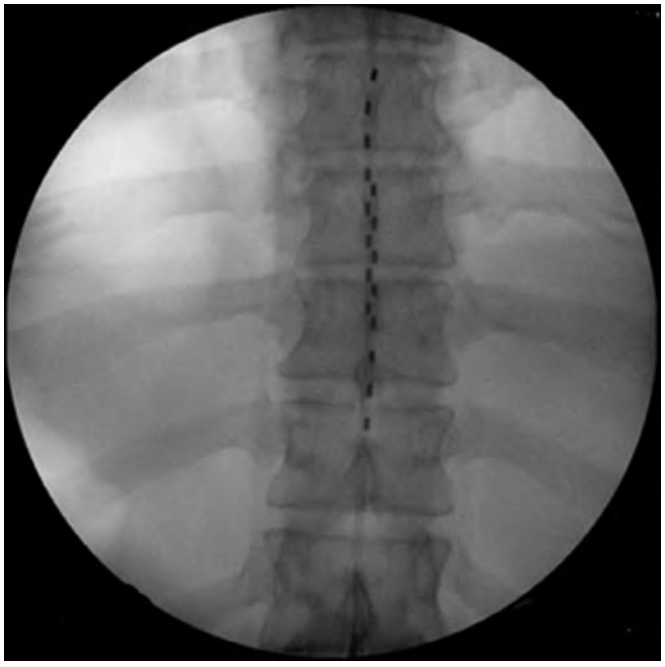
One advantage of SCS therapy is that patients can undergo temporary SCS trials. The time interval of SCS trials may vary between three and 30 days (most frequently seven to ten days in the United States). Based on the Neurostimulation Appropriateness Consensus Committee (NACC) Guidelines patients should be screened before the trial for the risk factors that may predispose them to complications from SCS, should be referred for a psychological evaluation to rule out any prohibitive psychological disorders that may hinder successful response to neuromodulation, and thorough history and physical examination should be performed (see Chapter 70).[34] If the patient is anticoagulated, the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines should be strictly adhered to minimize the risk of catastrophic epidural hematoma formation or any other bleeding.[35] Attention should be given to the patient's body habitus, as an increase in body mass index may affect procedural technique and predispose patients to postoperative infection. Spine imaging should be carefully reviewed to rule out structural instability that would warrant surgical attention and central canal stenosis that may preclude safe insertion of SCS leads.

The patient is positioned prone, weight-based antibiotics are administered 30–90 min prior to epidural space needle access, and if sedation is required, it should be minimal to facilitate patient-physician communication throughout the procedure.

After obtaining an anterior-posterior fluoroscopic image, the skin was anesthetized, and a Tuohy needle was advanced under intermittent fluoroscopic guidance toward the target interlaminar space. The needle should approach in a paramedian fashion parallel to the spinous process. The angle of approach should be between 30° and 45° to optimize the ability to steer the lead once it has been introduced into the epidural space. Contact may be made with the cephalad aspect of the lamina immediately below the intended epidural space. Next, the needle was advanced using a loss of resistance technique and intermittent lateral fluoroscopy. Once entry into the epidural space is confirmed via loss of resistance, the lead is threaded through the needle and introduced into the epidural space.

The lead was advanced under continuous fluoroscopy. After a satisfactory lead location was established (Fig. 71.1), the Tuohy needles were removed, and leads were secured in a fashion that suits the physician's preference. This may include suturing in place using manufacturer-provided anchoring devices, suturing to the lead itself, securing it using steri-strips and dressing only, or tunneling leading to possible prolonged trials (Fig. 71.2).

• **Figure 71.1A** Lateral fluoroscopic view illustrating interlaminar needle entry into the epidural space with eight contact spinal cord stimulation lead threading into the posterior epidural space. Note that undesirable anterior migration of the lead in the lateral fluoroscopic view would be evident if the lead were visualized running adjacent to the vertebral bodies at the anterior border of the neural foramen.



• **Figure 71.1B** Anterior-posterior fluoroscopic view of two eight-contact spinal cord stimulation leads in the midline, parallel orientation. Note the staggering of lead contacts to obtain maximal coverage from the top of T8 (left lead) to the top of T11 (right lead) vertebral bodies.

• **Figure 71.2** Two epidural leads tunneled 4–5 cm under the skin for possible prolonged trial. Notice that the Tuohy needle is inserted where a small stab wound was placed to facilitate tunneling. The duration of the trial may range from three to ten days, depending on patient response and physician preference. Beyond a ten day trial period, the risk of infection increases but may be mitigated by tunneling leads, as shown above.

Spinal Cord Stimulator Permanent Implant

Permanent implantation of the SCS system was performed in a sterile operating room setting. The patient was positioned prone in a similar fashion as described for the SCS trial procedure, with adequate padding to reduce normal lumbar lordosis (or cervical lordosis for cervical SCS implant). Anesthesia was administered, and the patient was prepped and draped in a sterile fashion. Intravenous antibiotics have been administered within 1 h of an incision.[34–36] AP fluoroscopy is utilized for guidance similar to lead placement during the trial. A vertical incision site is marked starting at the level of the intervertebral disc immediately inferior to the intended interlaminar insertion site and extending inferiorly three-four centimeters.

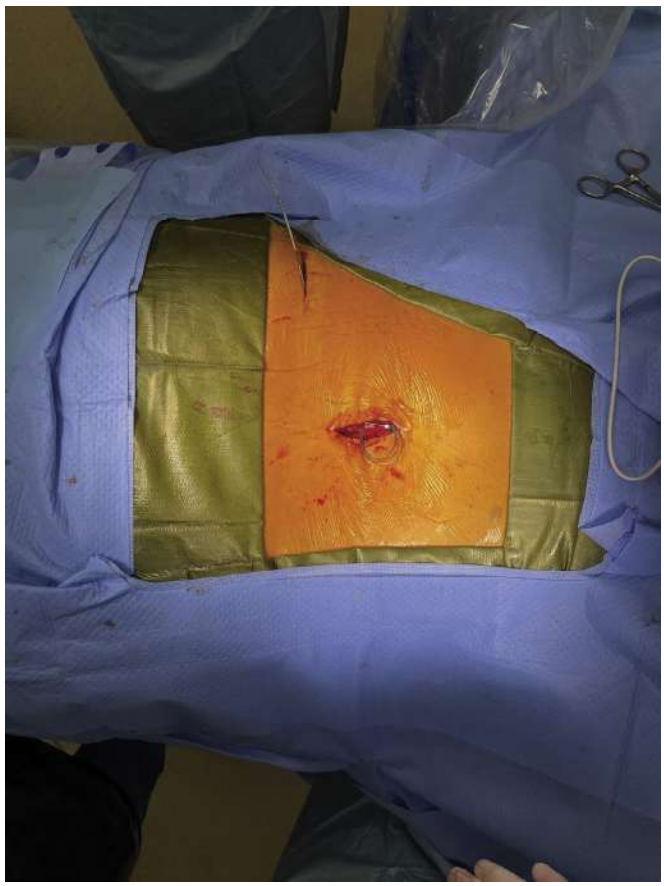
The epidural needles were removed, leaving the leads in place. The leads were then secured to the underlying fascia using the SCS manufacturer, which provided anchoring devices and non-absorbable sutures. A final fluoroscopy image was captured to ensure no lead migration occurred with needle removal and anchoring of the leads.

Another 4 cm horizontal incision was made, and blunt dissection was utilized to create a pocket for the implantable pulse generator (IPG) that was no more than 2 cm below the surface of the skin. This ensures the ability to charge the device effectively. It is essential to discuss the subcutaneous IPG location with the patient prior to implantation and examine the potential location while the patient is sitting.

Once the pocket has been created, and hemostasis has been achieved, the leads must be tunneled from the midline incision to the pocket (Fig. 71.3). The wounds were irrigated and closed in a layered fashion using simple interrupted absorbable sutures.

Complications

The SCS device-related infection rate was estimated to be 3.11% based on logistic regression (n=6615) over a 12 month postoperative period.[36-38] It is most commonly seen at the IPG pocket site. Lead migration has been reported as a possible complication of SCS, occurring at a rate of approximately 2.1%–12% of implants depending on the reference source.[39,40] Pocket site discomfort has also been noted with some frequency.[34,39] Other less common complications that have been described include electrode fracture, IPG failure, and CSF leak following a dural puncture, among others.[36–41]



• **Figure 71.3** Subcutaneous tunneling of two leads from the midline incision to the generator pocket. Notice formed lead loop at the midline incision site, which will be used as a strain relief loop, one of the strategies on how to minimize lead migration from the epidural space.

Clinical Outcomes

Traditional (0–1200 Hz) has been demonstrated to be a superior treatment option for patients with failed back surgery syndrome compared to conventional medical management or reoperation.[2,3] In addition to traditional SCS being more efficacious in improving pain scores and quality of life, it was also found to be less costly than long term medical management or reoperation for failed back surgery syndrome.[2,3,42] Low frequency SCS has traditionally relied on paresthesia coverage overlapping the distribution of a patient's pain. Compared to traditional tonic stimulation, some studies have demonstrated better or similar responses to sub-perception stimulation at 1000–1200 Hz.[9,10]

Burst stimulation is another recently studied waveform with considerable evidence to support its use. A "burst" is characterized by a five-pulse train with an internal frequency of 500 Hz delivered at 40 Hz utilizing a passive recharge pattern and waveform.[11,43,44] It was first described by De Ridder et al. in 2013.[45] Deer et al. conducted a large randomized controlled trial (RCT)

(SUNBURST) in which 100 patients were randomized to receive traditional or burst stimulation for 12 weeks. After the 12 week period, the patients were crossed over from traditional stimulation to the burst stimulation group for an additional 12 weeks. Burst stimulation was superior to traditional tonic stimulation, with slightly better average pain scores ($P < 0.017$). Of note, at one year post-implant, 68.2% of patients preferred burst stimulation.[11]

There is substantial level 1 evidence to support the efficacy and durability of high frequency (10 kHz) SCS for treating back and leg pain and the superiority of high frequency stimulation over traditional stimulation.[4,5] In a large prospective randomized control trial published in 2015 (SENZA-RCT), the response rates of 171 patients who were implanted with either a 10 kHz or traditional low frequency 2–1,200 Hz SCS system to treat back and leg pain were compared. At 12 months post-implantation, both groups had sustained response, but in the 10 kHz therapy group, 80% of patients reported more than 50% pain relief, compared to less than 50% responders in the traditional SCS group. Mean back pain was reduced from Visual Analog Scale (VAS) of 7.4 +/- 1.2–2.5 (67% decrease) in the 10 kHz group versus being reduced from 7.8 +/- 1.2–4.3 (44% decrease) in the traditional SCS group. These results were noted to be durable through a 24 month follow up, with a 76.5% ongoing responder rate in the 10 kHz SCS group versus a 49% responder rate in the traditional SCS group.[5] Evidence for the efficacy of 10 kHz SCS has been further substantiated in two large randomized prospective studies on chronic nonsurgical back pain patients and those with peripheral neuropathy in diabetes.[46,47] This therapy is currently the only one supported by three large prospective RCTs.[5,46,47] Furthermore, a recently published retrospective study measured 10 kHz SCS ability as the rescue therapy in patients who were previously implanted and failed conventional, low frequency SCS systems. Of the 105 patients analyzed, 81% experienced greater than 50% pain relief after transitioning from the traditional (less than 1200 Hz) to 10 kHz SCS.[48]

Closed-loop SCS was recently trialed in a multicenter, double-blind, parallel-arm RCT that enrolled 134 patients. The participants were randomized to the control group, which received fixed output, open-loop stimulation, or the experimental group that received ECAP-controlled closed-loop SCS. The primary outcome measure was the percentage of patients who achieved >50% pain relief in the back and legs at three and 12 months. The closed-loop group had an 82.3% responder rate at three months and 83.1% at 12 months, compared to the open-loop group, which had a responder rate of 60.3% and 61% at three and 12 months, respectively.[7]

DRG stimulation uses stimulation waveforms similar to traditional SCS, via stimulation lead(s) placed near the DRG and relatively low frequencies at approximately 20 Hz. The study that helped facilitate approval of the DRG stimulation system in the United States (ACCURATE study) randomized patients to DRG stimulation compared to traditional SCS therapy. The study was performed on 152 subjects with lower extremity pain due to mononeuropathies and complex regional pain syndrome (CRPS). DRG stimulation provided a significantly greater level of treatment success with ≥50% pain relief in 81.2% of patients vs. SCS (55.7%). Longevity of the pain relief was documented at 12 months post-implant as well.[6]

Peripheral Nerve Stimulation (PNS)

While the focus of this chapter was SCS, it should be noted that other central and extraspinal neural targets have been successfully stimulated to produce analgesia. PNS as a modality for the treatment of pain predates SCS in a short time, with both being introduced to the modern medical community in the mid-1960s by Wall and Sweet as well as others.[49]

PNS includes:

- open surgical implantation of electrodes overlying target nerves outside the central nervous system (CNS);
- percutaneous image-guided implantation of electrodes; and
- stimulation of terminal nerve endings in the receptive field of a larger target nerve, PNFS, or field stimulation.

Over the last ten years, there has been a mounting wealth of evidence supporting the use of PNS in the treatment of focal neuropathic pain and several other conditions, including post-amputation pain syndrome, post-surgical pain, chronic shoulder pain, chronic low back pain, and craniofacial disorders among others.[50–57] A variety of stimulation parameters have been utilized, from traditional paresthesia-based programming to high frequency sub-perception stimulation at 10 kHz. Qualitatively, the evidence in the medical literature has also improved with the recent completion of multiple prospective randomized, double-blind placebo-controlled clinical trials demonstrating positive results.[58–60]

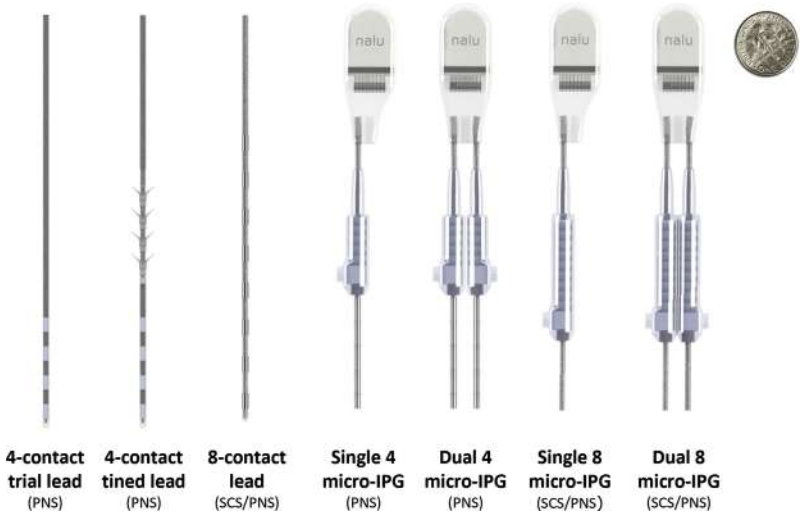
There have been three major developments that have led to the resurgence of PNS.

1. A shift from open surgical exposure of the target nerve to percutaneous implant techniques was first introduced by Weiner and Reed in the 1990s.[61]
2. Use of ultrasound guidance for lead implants.[62,63]
3. Development of devices specifically designed to be used in the periphery (illustration of leads from Nalu; Fig. 71.4) and SPR Therapeutics (Fig. 71.5) to address many of the shortcomings associated with adapting SCS devices for use outside the spinal canal, that is, lead migration, lead fracture, battery failure, surgical site infection, and neurologic injury.[64]

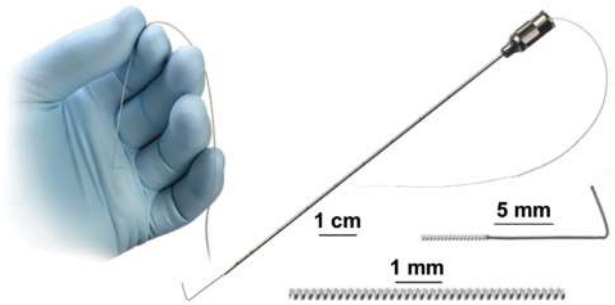
These advances have led to a growth in the number and variety of targeted conditions. However, the resulting reduction in the invasiveness of the implant procedure, moving away from open surgical exposure to a more commonly used percutaneous approach, has caused a concomitant shift in the background and training of implant providers. Surgical training, while helpful, is no longer a requisite.

Historically, the PNS has followed the same pattern of trial as permanent implantation as SCS. However, temporary percutaneous PNS (PPNS) has a growing body of literature supporting its use and demonstrating long term efficacy in various pain syndromes, including post-amputation pain, post-stroke shoulder pain, and chronic low back pain.[5,65,66] Enduring clinically significant pain relief has been shown in several studies using PPNS with an indwelling time of four to eight weeks. Lasting reductions in disability, pain interference and opiate requirements have been demonstrated as well.[67] The proposed mechanism of action for this sustained analgesia involves focal and robust physiologic peripheral signaling that is believed to be responsible for the reversal of maladaptive central plasticity of chronic pain.[68]

The current state of PNS is a combination of traditional techniques and newly developed strategies. First suggested more than 40 years ago, occipital nerve stimulation as a treatment for craniofacial pain is one of the more common uses of PNS to this day despite failure to meet primary endpoints in large multicenter clinical trials.[69-71] More recently, vagal nerve stimulation, an open surgical procedure long used to address seizures and refractory depression, has been reinvented as a non-invasive procedure to treat headache disorders.[55,56,60] The relatively newer concept of restorative neurostimulation targets the lumbar medial branch nerves to elicit episodic contractions of previously impaired



• **Figure 71.4** Development of leads that are amenable to implant outside the spinal canal and miniaturization of stimulator components has been an important development in peripheral nerve stimulation (PNS), used with permission from Nalu Neurostimulation System. *SCS*, Spinal cord stimulation.

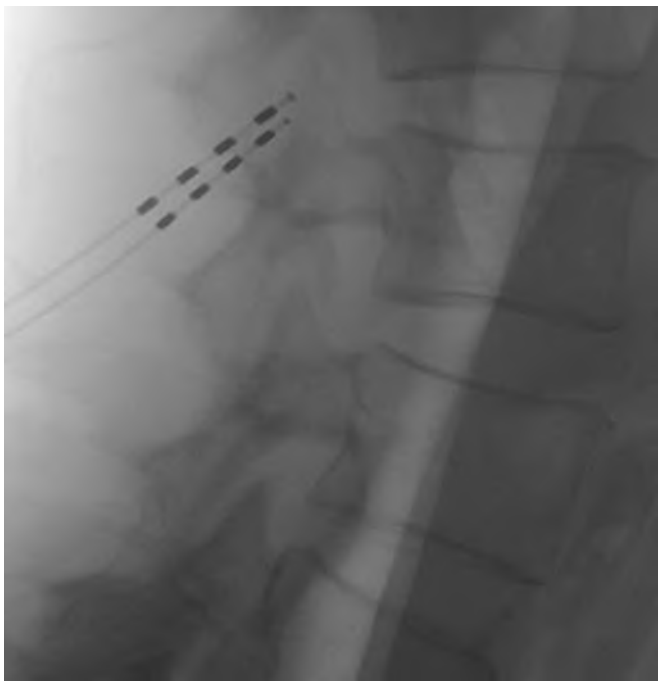


• **Figure 71.5** Fine-wire, open-coiled lead for percutaneous peripheral nerve stimulation, used with permission from SPR Therapeutics.

lumbar multifidus musculature in chronic low back pain patients (Fig. 71.6).[72] It is supported by a multicenter prospective, randomized, double-blinded clinical trial with a two year follow up in the peer-review process. Continued deciphering of the pathophysiologic mechanisms of therapeutic targets coupled with steady progress in device design and ergonomics, along with minimally disruptive delivery of the therapy, promises specifically tailored treatment and improved outcomes for PNS.

Motor Cortex and Deep Brain Stimulation

Motor cortex and deep brain stimulation have been explored to treat highly refractory neuropathic pain syndromes, including central pain, deafferentation syndromes, and trigeminal neuralgia.[73] Deep brain stimulation (DBS) has become a widely used technique for movement disorders and much less so for painful indications, although there have been many case reports on the treatment of highly refractory central pain syndromes.[74] Unfortunately, a multicenter study, promoted by the Food and Drug Administration, showed negative results of DBS therapy in the treatment of neuropathic pain.[75] These findings hinder the use of DBS in clinical practice in the United States, leaving only



• **Figure 71.6** Permanently implantable restorative neurostimulation for axial low back pain, used with permission of Mainstay Medical.

class III level evidence for DBS for phantom limb pain, trigeminal neuralgia, and other peripheral nerve pain syndromes. Since its introduction in the early 1990s, motor cortex stimulation (MCS) for the treatment of pain has been supported by several blinded RCTs (Class I evidence), including a 2009 clinical trial that enrolled 16 participants who had neuropathic pain related to peripheral lesions. The 12 monthly follow up included VAS, Brief Pain Inventory, McGill Pain Questionnaire, and Sickness Impact Profile scores. VAS and Sickness Impact Profile scores were significantly improved one year post-implantation.[76] Repetitive

transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are promising non-invasive cortical stimulation strategies for neuropathic pain treatment whose mechanisms of action are believed to be shared with MCS.[77–79]

Summary

Recent advances in neuromodulation, including efficacious new waveforms and expansion of indications, solidified clinical usage of SCS, PND, DBS, and MCS. High frequency 10 kHz SCS, closed-loop type of SCS, DTM, and DRG stimulation provided significantly improved outcomes when used for the treatment of chronic pain and may result in a significant increase in the utilization of SCS in the years to come. Similarly, improved expertise in PNS guidance using ultrasound increases the usage of this therapy, resulting in a higher level of evidence. DBS and MCS technologic advancements and new indications follow a similar suit. When this chapter was written, several large prospective trials were being conducted in neuromodulation, making this therapeutic area one of the most promising in neuroscience.

Key Points

- The major mechanisms of traditional low frequency SCS include activation of the gate control mechanisms, blockade of pain conduction via the spinothalamic tract, supraspinal sympathetic suppression, and activation or release of neuromodulators.
- Blockade of supraspinal sympathetic mechanisms by SCS results in an increase in peripheral blood flow with transitory inhibition of sympathetic vasoconstriction.
- Activation or release of neuromodulators such as GABA in the dorsal horn, glycine release in the extracellular space of the spinal cord, and inhibition of glutamate and aspartate release in the dorsal horn are additional mechanisms for pain control.
- SCS affects heart function by reducing intrinsic cardiac nervous system activity, preemptive suppression of a marked increase in sympathetic outflow, and a decrease in the frequency of arrhythmias in ischemic hearts.
- SCS improves ischemic pain in the extremities by a vasodilator effect via CGRP, peripheral prostacyclin release, and neuronal increase of nitric oxide.
- In an acute neuropathic pain model in rodents and mammals, the DTM type of SCS provided superior thermal and mechanical hypersensitivity suppression compared to low and high frequency SCS.
- Dorsal root ganglia stimulation acts directly on the development of neuropathic pain through inhibition of hyperexcitability and spontaneous ectopic firing of neuronal cell bodies contained within the DRG.
- In patients with chronic pain of the trunk and/or limbs, burst stimulation was noted to be superior to traditional tonic stimulation, with slightly better average pain scores. At one year post-implant, more patients preferred burst stimulation.
- There is substantial evidence to support the efficacy and durability of high frequency (10 kHz) SCS for treating back and leg pain and the superiority of high frequency stimulation over traditional stimulation.
- In patients with chronic back and leg pain, closed-loop stimulation was found to be superior to open-loop stimulation.
- The development of ergonomically designed devices in the periphery, combined with the use of ultrasound guidance for implantation, has facilitated a resurgence of the use of PNS for the treatment of many chronic painful conditions.

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Intrathecal Drug Delivery

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Intrathecal drug delivery for the treatment of pain is an outgrowth of pioneering research into spinal cord mechanisms and receptors that modulate nociceptive signal transmission to and within the central nervous system. Since the 1970s, researchers have identified the peptide substance P in small dorsal root ganglion cells[1] and observed that opioids would produce analgesia.[2] These findings, as well as the observation that substance P release evoked from C fibers is blocked by morphine,[3] marked the beginning of the current trend toward focusing on the selective regulation of spinal afferent processing. Since then, there has been much research in this area, leading to the widespread use of intrathecal therapy to treat chronic intractable pain. Although this therapy has proven extremely beneficial to many patients, it is also associated with high costs, high maintenance, and risks requiring careful patient selection. The first section focuses on the patient selection, technologies used for chronic intrathecal drug delivery, system implantation, and troubleshooting. The second section reviews the medications used in intrathecal drug delivery systems.

Patient Selection, Trialing, and Implantation

Intraspinal Drug Delivery Techniques

There are essentially three methods of intraspinal drug delivery: (1) externalized systems, (2) partially externalized systems, and (3) totally implanted systems. The selection of the technique will depend on the goal of therapy, ranging from short term intrathecal trialing to long term therapy to treat chronic pain. Each technique has associated risks and costs, which must be considered when selecting the technique.

Externalized Systems

An externalized intrathecal catheter can be used for trialing intrathecal drugs or for short term therapeutic infusions. Such a system is best for infusions lasting hours to days but has been successfully used for longer term delivery in terminally ill patients lasting a few weeks. The use of an externalized catheter raises the concern for a local infection at the catheter exit site or that the catheter may serve as a conduit for either epidural or intrathecal spread of infection. Using a strict aseptic technique for catheter insertion can minimize the risk of insertion site infection, and the placement of a chlorhexidine impregnated catheter patch at the insertion site further reduces this risk (Fig. 72.1). There is no evidence that systemic antibiotics prevent these infections. In a terminally ill patient with a very short life expectancy, the risk-benefit ratio may favor the use of an externalized catheter for intrathecal drug delivery. Some practitioners tunnel these catheters under the skin for some distance to provide stability and reduce the likelihood of inadvertent catheter withdrawal. Currently, the United States Food and Drug Administration (FDA) has not approved any externalized intrathecal catheters, and it is common to use epidural or lumbar drain catheters for this purpose.

Partially Externalized Systems

Partially externalized systems are those in which the intrathecal catheter is tunneled and connected to a subcutaneous port. A needle then accesses the port percutaneously, and medication is delivered with tubing connected to an external pump. Compared to an externalized system, this permits greater patient freedom of movement and reduces the risk of inadvertent catheter removal. Partially externalized systems are intended for single bolus injections. There continues to be a risk of colonization and infection of the port pocket with prolonged or repeated needle access. These systems have limited application for long term, continuous intrathecal drug delivery.

Implanted Intrathecal Infusion Pumps

Totally implanted systems are the most common and have the catheter and pump completely internalized by surgical implantation. These are used for long term infusions and afford the patient much greater freedom of movement. A totally implanted system is more expensive and requires a more invasive surgical procedure than an externalized or partially externalized system. Although it is generally recommended that implanted pumps be reserved for patients with a life expectancy of greater than six months,[4,5] this therapy may improve quality of life in patients with life expectancy as low as two to three months. However, patients with a life expectancy of fewer than six months should be carefully selected.

There are two main types of intrathecal infusion systems, fixed-rate and variable-rate programmable pumps. All implanted pumps have two percutaneous access ports. One port is for refilling the drug reservoir, and there is a separate intrathecal catheter access port for bolus injection through, or aspiration from, the catheter. The infusion systems are generally implanted in the lower abdominal subcutaneous fat and connected to a catheter, which is tunneled subcutaneously around the abdominal wall into the intrathecal space.[6,7] However, the pumps may also be implanted subcutaneously in the lower back in selected patients

Drug/Dose	Hold Prior to Needle/Catheter Placement	Restart after Neuraxial Placement
Heparin SQ	1 hour	1 hour
Enoxaparin 40 mg SQ/day	12 hours	2 hours
Enoxaparin > 40 mg SQ/day	24 hours	2 hours
Warfarin	5 days & check INR < 1.3	Same day
NSAIDS/Aspirin	Not necessary	—
Clopidogrel (Plavix)	7 days	Same day
Ticlopidine (Ticlid)	14 days	Same day

• **Figure 72.1** Chlorhexidine impregnated patch, BioPatch, Johnson & Johnson.

• **Figure 72.2** Codman 3000 fixed-rate infusion pump, Codman & Shurtleff, Inc.

• **Figure 72.3** Syncromed II intrathecal pump, Medtronic, Inc.

(see the discussion that follows). The septum puncture life of the percutaneous refill port is very high: 500 punctures for the most commonly used pump, the Medronic Synchromed II pump. It would be unlikely to reach this number of punctures during the life of the pump (5.5 years for the Synchromed II).[8]

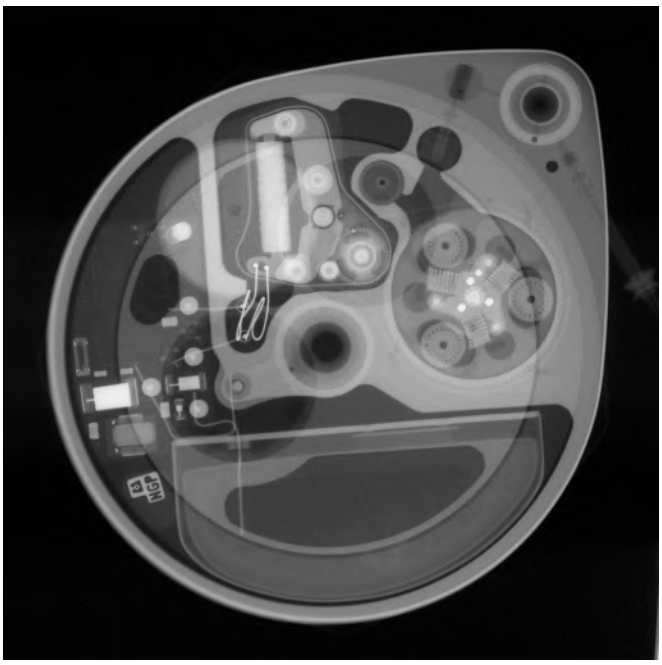
The first intrathecal pump, manufactured by Shiley Infusaid, became commercially available in 1982.[9] The Infusaid and other early pumps were non-programmable fixed-rate infusion systems. These pumps were simple devices without batteries, in which pressurized gas pushes the drug from a reservoir through a valve and into the catheter. The kinetic energy of the pressurized gas is increased every time a new drug is injected into the reservoir. The chief advantage of these pumps is the simplicity of design and lack of batteries. Unfortunately, they cannot vary the dose delivered without changing the concentration of the drug in the reservoir. The last of these pumps, the Codman 3000 (Fig. 72.2), was discontinued in 2018. Fixed infusion rate pumps have not been used with any frequency in the United States for many years. However, some of these pumps may still be implanted and functional in patients since there are no batteries; thus they never require replacing because of battery failure. The Codman pump was available in different sizes and various flow rates. The flow rate is controlled by a flow restrictor. Flow rates may vary for different drugs, drug combinations, and especially with high drug concentrations, based on differences in viscosity.[10] In addition, changes in body temperature and atmospheric pressure will change flow rate by affecting the gas pressure within the system.

Programmable pumps allow the clinician to vary infusion rates to increase or decrease the dose without changing the concentration of the drug or drugs in the pump. The original programmable pump was the Medtronic Synchromed, first introduced in 1991.[11] This device was upgraded to the Medtronic Synchromed II (Fig. 72.3), which allows patient-controlled intrathecal bolus dosing via a remote-control device. The Synchromed II uses a peristaltic roller system (Fig. 72.4) to move the drug from the reservoir to the implanted intrathecal catheter. The Synchromed II is available in 20 mL and 40 mL reservoir sizes and is FDA approved for baclofen, morphine, and ziconotide.

The other programable intrathecal pump on the market is the Flowonix Prometra II implantable pump. Similar to the older non-programmable pumps, the original Prometra and newer Prometra II use a pressurized gas chamber as the driving force. Unlike those older fixed-rate infusion pumps, a programmable flow-metering valve allows for a variable drug delivery rate.[12] The Prometra pump's low energy requirement is its main advantage. Since the batteries are used to control the electronics only, not to pump the drug, the battery has a ten-year life span before the need to surgically replace the pump. The Prometra is available in a 20 mL reservoir and is FDA approved for morphine. The issues with variable flow resulting from viscosity, temperature, and residual reservoir volume have been addressed by the advanced flow-metering valve.

Intrathecal Pump Magnetic Resonance Imaging (MRI) Compatibility

Both the Synchromed II and Prometra pumps are MRI conditional. However, the conditions for MRI management are different between the two.[13,14] As discussed above, the Synchromed



• **Figure 72.4** Synchromed II internal structures, Medtronic, Inc.

pump is driven by a peristaltic pump that can be programmed to rotate at different rates to adjust drug daily dose. When in the MRI, the peristaltic rotor will suspend in the magnet and stop the flow of the drug. When removed from the magnet, the rotator will restart the drug flow as programmed. The MRI might result in a permanent pump stall if the rotor does not resume functioning. The risk of a permanent pump stall increases as the pump moves closer to a 90-degree position in the magnet. This may occur in patients with the pump flipped 90 degrees to normal placement in the abdominal wall pump pocket. Pumps in the traditional position within the abdominal wall are closer to the 0-degree position with a lower risk.[14]

The Prometra pumps have a flow-metering valve that will move into the fully open position while in the MRI. Since the pump reservoir is under positive pressure, this would result in immediate release of the entire pump reservoir contents resulting in overdose. Therefore in the original Prometra pump, it is critical to remove all drugs from the reservoir prior to an MRI. The Prometra II pump has a safety mechanism that if the flow-metering valve abruptly opens, a secondary valve closes, thus stopping the flow. The pump will not restart until this secondary valve is reset. Despite the secondary valve's safety measure, the manufacturer's recommendations for MRI compatibility with the Prometra II pump are to remove the contents of the drug reservoir prior to an MRI.[14]

Patient Selection

Pain Type

Intrathecal drug delivery systems (IDDSs) are reserved for treating severe and refractory pain in two types of patients: those with cancer pain and those with non-cancer pain who have failed all conservative therapies.[15] The cost and invasive nature of IDDSs necessitate a careful evaluation to determine whether each individual patient is appropriate and likely to achieve benefit. A thorough assessment includes an evaluation of pain-generating pathologic conditions, medical comorbidities, psychosocial issues, patient compliance history, economic and healthcare coverage, and anatomic and technical considerations.[16]

In advanced stages of cancer, the prevalence of pain exceeds 60%. One-third of those patients report moderate to severe pain.[17] Comprehensive medical management (CMM) can significantly reduce pain and manage the adverse effects of opioids and other analgesics.[18] Despite aggressive therapy, some patients continue to endure severe pain. Others are unable to tolerate systemic opioids because of toxicity. A 2002 multi-center randomized trial compared CMM alone versus CMM plus an IDDS. They found that cancer patients receiving CMM plus an IDDS had reduced pain, fewer drug toxicities, and prolonged survival than controls.[18] Patients with significant toxicity or with refractory pain that has been inadequately controlled by the systemic administration of opioids and other analgesics are potential candidates for an IDDS (Table 72.1).[19] Intrathecal therapy may be especially valuable in patients with neuropathic pain from tumor invasion of neural

TABLE 72.1 Clinical Studies of Intrathecal Therapy for Cancer-Related Pain

Study	Number of Subjects	Type/Duration	Details	Efficacy
Smith et al. 2002[20]	200	RCT/four weeks	Advanced cancer pain; CMM (99) vs. IDDS (101)	IT plus CMM improved pain and reduced opioid adverse effects
Staats et al. 2004[21]	111	RCT/11 days	Refractory pain because of cancer or AIDS; ziconotide (71) vs. placebo (40)	IT ziconotide significant improvement in pain scores vs. placebo
Rauck et al. 2003[22]	119	Prospective Observational; up to 16 months	Refractory cancer pain; addition of IT morphine	Significant reduction in pain intensity and systematic opioid use
Mercadante et al. 2007[23]	55	Prospective Observational; up to six months	Advanced cancer pain; addition of IT morphine + levobupivacaine	Improved pain, decreased oral opioid, decreased opioid adverse effects
Dupoiron et al. 2012[24]	77	Prospective Observational; 90 days	Refractory cancer pain; ziconotide + morphine, ropivacaine, and/or clonidine	Improvement in numeric rating scale pain scores
Brogan et al. 2015[25]	58	Prospective Observational; 14–82 days	Refractory cancer pain; addition of IT analgesics	Decrease in numeric rating scale pain scores; decreased percentage with severe pain

plexuses, unstable pathologic fractures, painful impending spinal cord compression, and visceral tumors with or without autonomic dysfunction that results in gut dysmotility.

In patients with a life expectancy of less than two to three months, a percutaneous catheter and external pump can be used. These patients may be discharged from the hospital with hospice care or home-health services for the care of the catheter and infusion if appropriate services are locally available.

For the patient with chronic non-cancer pain, a comprehensive evaluation to establish the cause of the pain should be performed as part of the decision process regarding whether an intrathecal pump is appropriate. The evaluation should include a detailed history, physical examination, radiologic studies, and assessment of prior therapies and their outcomes.[26–28] Many diagnoses and painful conditions may be amenable to intrathecal drug delivery in certain cases. These include neuropathic syndromes, such as spinal cord injury, diabetic peripheral neuropathy, complex regional pain syndrome, postherpetic neuralgia, and phantom limb pain. Additionally, mixed nociceptive and neuropathic conditions, such as post-laminectomy pain syndrome or chronic pancreatitis, and nociceptive pain conditions, such as chronic vertebral compression fractures and severe spinal degeneration, may be appropriate for an IDDS in some circumstances after thorough patient selection and discussion.[16,28,29]

Implanted drug delivery therapy should be reserved for those patients who are refractory from more conservative treatment. A stepwise approach starting with the least invasive and costly therapies is recommended.[15,16] This may begin with exercise programs, relaxation techniques, and over-the-counter analgesics. Subsequent steps include adjuvant analgesics, muscle relaxants, physical therapy, and psychological therapies. More invasive therapies include neuraxial somatic and sympathetic blocks and spinal cord stimulation. The top tier of this stepwise treatment pyramid is reserved for the most invasive therapies, including intrathecal drug delivery and neuro-destructive procedures, such as cordotomy, myelotomy, and dorsal rhizotomy.[28,30] There are few controlled trials of intrathecal therapy for chronic non-cancer pain. However, observational studies suggest such therapy can provide pain relief in certain patients who have failed to achieve relief with more conservative treatments (Table 72.2).[31,32] Determining the efficacy of long-term intrathecal drug therapy remains one of the greatest challenges in chronic non-cancer pain management. One of the reasons for the lack of randomized controlled trials is that the high cost and invasiveness of such treatment pose ethical challenges in designing a double-blind, placebo-controlled study. Therefore one can only rely on the retrospective reviews of patients receiving this therapy and attempt to make conclusions on the efficacy of this treatment. Many studies have attempted to determine the efficacy of long-term intrathecal morphine therapy based on the classification of the pain. However, a review of these articles reveals large discrepancies in pain classification between studies. Because pain is often multifactorial (e.g. failed back syndrome versus HIV neuropathy versus complex regional pain syndrome), it is difficult to determine what pain syndromes are the most responsive to this therapy and have long-term benefits.

Patient Comorbidities

The aging, chronic pain patient may experience some of the same age-related comorbidities as any individual. Many of these comorbid conditions can complicate the implantation and use of an intrathecal pump. These medical issues and their potential interaction with intrathecal therapy must be considered during the patient selection process.

TABLE 72.2 Clinical Studies of Intrathecal Therapy for Non-Cancer Pain

Study	Number of Subjects	Type/Duration	Details	Efficacy
Winkelmuller et al. 1996[33]	120	Retrospective; six months to 5.7 years follow up	Mixed neuropathic/nociceptive pain; morphine, bupivacaine, hydromorphone	74% reported improvement in pain, averaging a 58% reduction
Anderson et al. 1999[34]	30	Retrospective	Failed back surgery; rotation from morphine to hydromorphone because of adverse effects or poor pain control	37% had improved pain control; the majority with decreased adverse effects (nausea, pruritis, edema)
Kumar et al. 2001[35]	25 trialed 16 implanted	Prospective, single-center, non-randomized	Non-malignant pain; morphine; follow up 13–49 months	Trial 64% with >50% pain reduction; implant avg reduction 57.5% at final follow up
Rainov et al. 2001[36]	30 trialed, 26 implanted	Prospective, single-center, non-randomized	Failed back surgery syndrome; polydrug infusion of morphine + clonidine, bupivacaine, or midazolam; mean follow up 27 months	Average pain intensity 8/10 to 3/10, remained in the range of 3–5/10 throughout follow up
Deer et al. 2004[37]	166 trialed, 136 implanted	Prospective, non-randomized, multi-center registry	Mechanical neuropathic, mixed low back/leg pain. Trialing and implant for non-malignant pain; follow up 12 months	93% trial success; 82% implanted; 48% reduction in the low back; 32% for leg pain at 12 months
Rauck et al. 2006[38]	220	Randomized, double-blind, placebo controlled	Ziconotide slow titration over three weeks; 112 ziconotide, 108 placebo	Statistical significance for ziconotide over three weeks; higher adverse effects

Diabetes Mellitus

Diabetes mellitus affects over 8% of the United States population and nearly 27% of those over 65 years.[39] Patients with diabetes experience poor wound healing and suffer from an increased incidence of surgical site infections.[40–42] Implantable devices pose a special risk of surgical wound infections. With implantable intrathecal pumps, wound infections have been found to be the most common device-related complication.[41] Patients with diabetes, especially if blood glucose control is poor, should be counseled on the increased risk, and implanters should check a hemoglobin A1C prior to surgical implant and consider postponing surgery for an A1C >8.[41]

Anticoagulant Therapy

Patients on anticoagulant therapy are at increased risk of epidural hematoma formation after placement or removal of epidural or spinal catheters.[43,44] Additionally, multiple new anticoagulant agents have made the management of anticoagulation for invasive pain procedures more of a challenge. Many of these agents carry specific warnings related to spinal injection procedures but may not provide clear guidance regarding perioperative or peri-procedural management. A group of chronic pain societies, including the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain, have published guidelines regarding the management of drugs that affect coagulation in the setting of invasive pain procedures (Box 72.1).[44] They divide pain procedures into three risk categories: low, intermediate, and high. The implantation of intrathecal pumps is considered by this guideline to be a high-risk procedure. Scattered case reports of anticoagulant therapy restarted after implantation of intrathecal pumps offered no clear evidence for or against the safe use of intrathecal pumps in these patients.[16]

Infections

Any active infection puts the patient at risk of a surgical site infection that may be superficial or deep into the pump pocket. While a superficial surgical site infection may be successfully treated medically, a pump pocket infection is virtually impossible to clear with antibiotic therapy and will require explanting the entire pump and catheter system. Any active or chronic bacterial or fungal infections, particularly with non-cancer pain patients, should be regarded as a contraindication to implantation.

Pulmonary Disease

More than 18 million Americans have obstructive sleep apnea (OSA).[45] In addition to the risks of carbon dioxide retention and both systemic and pulmonary hypertension, the OSA patient has increased sensitivity to the respiratory depressant effects of opioids.[46] There are no studies of intrathecal opioid use in OSA patients. However, case reports suggest that chronic use of oral opioids in those with OSA increases apnea duration and hypoxia severity.[46] Chronic obstructive pulmonary disease (COPD) also results in carbon dioxide retention and increased risk of respiratory depression with the administration of opioids. A retrospective case-controlled study of postoperative COPD patients administered opioids found an increased risk of respiratory events (odds ratio [OR] 5.09; 95% confidence interval [CI]) than patients without chronic lung disease.[46] Most of these events occurred within 24 h of surgery. The long-term risk of intrathecal opioid administration in patients with severe pulmonary disease is unknown. However, known risks of perioperative opioid administration in this population warrant careful monitoring during trialing as well as after implantation and initiation of therapy.

Additionally, patients who are chronic smokers are at increased risk of surgical site infections. The Polyanalgesic Consensus Conference (PACC) published several guidelines regarding intrathecal pump implantation and management. They recommend smoking cessation two months prior to elective intrathecal pump implant.[41]

Psychological Screening

The Centers for Medicare and Medicaid Services require a psychological assessment prior to the implantation of spinal cord stimulator systems. No such requirement exists for IDDS. Although not required, it is widely accepted that a pre-procedure psychological assessment is warranted and is at least as important if not more important for appropriate patient selection for an IDDS as spinal cord stimulation for non-cancer pain treatment.[5,15,16,26,27] Ideally, a psychological evaluation would aid in predicting positive response to an implantable therapy. In reality, there is limited evidence regarding the efficacy of psychological screening to predict long-term success. Psychological counseling should be used to establish well-care and goal setting and counsel on unlikely or irrational

• BOX 72.1 Summary of American Society of Regional Anesthesia (ASRA) Neuraxial Analgesia Anticoagulation Guidelines for High-Risk Procedures (Intrathecal Pump Implantation)

Drug/Dose	Hold Prior to Pump Implantation	Restart After Implant
Heparin SQ (BID or TID)	24 h	6–8 h
Enoxaparin 40 mg SQ/day	12 h	12–24 h
Enoxaparin >40 mg SQ/day	24 h	12–24 h
Coumadin	Five days & check INR<1.3	6 h
NSAIDS	Five half lives	24 h
Aspirin	Six days primary prophylaxis; shared decision-making secondary prophylaxis	24 h
Clopidogrel (Plavix)	Seven days	12–24 h
Prasugrel (Effient)	Seven to ten days	24 h
Ticagrelor (Brilinta)	Five days	24 h
Dabigatran (Pradaxa)	Four days	24 h
Rivaroxaban (Xarelto)	Three days	24 h
Apixaban (Eliquis)	Three days	24 h

(From Narouze S, Benzon H, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (second edition): guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med.* 2018;43:225–262).

patient treatment expectations. Much of the literature in this area concerns implantable spinal cord stimulators, and it is from this body of literature that guidelines regarding the use of psychological evaluation for IDDS have been extrapolated.[5,15,16,26,27]

The presence of suicidal or homicidal ideation, uncontrolled depression, active psychosis, severe cognitive deficits, and active drug abuse are contraindications to implantation. In a study by Celestin and colleagues, certain psychological factors and traits were associated with poor analgesic outcomes after implantation. These include somatization, depression, anxiety, and poor coping skills.[47] However, a study by Doleys and Brown found that those with a mild abnormality on the Minnesota Multiphasic Personality Inventory (MMPI) personality profiles had better long term analgesic efficacy than those with more normal scores.[48] Consensus guidelines have recommended the use of some form of psychological assessment in the selection process for IDDS candidates but caution against using the results to categorically rule out implantation in patients with psychological issues.[16,26,27]

The psychological evaluation should be used to identify factors that may affect the outcome of a trial or long term therapy, either positively or negatively. In addition to identifying severe psychopathologic conditions, the screening examination can evaluate for cognitive deficits, coping mechanisms, social supports, patient expectations, and comprehension of treatment goals that may affect therapy. This screening may also identify the need for psychological treatment that can improve the outcome of therapy. The psychologist should not be asked to give "clearance" but rather act as an additional source of information about whether IDDS therapy is appropriate, the patient has rational expectations, and this therapy is likely to succeed for an individual patient.

Trialing

Some type of therapy trial prior to permanent system implantation has been commonly performed and is often required by insurance payers such as Medicare. Trial options include a single bolus intrathecal injection or a continuous infusion via the percutaneous intrathecal or epidural catheter. The PACC guidelines on trialing for intrathecal therapy note that there is no data to suggest one trialing method is superior to another.[27] Further, the data are limited, suggesting that trialing can accurately predict efficacy after implantation.[16] While the PACC guidelines recommend a trial for non-cancer pain, an earlier expert consensus statement regarding guidelines for selection of patients for non-cancer pain recommended against the requirement of a pre-implant trial because of the trial's unsubstantiated predictive value.[16,27]

The selection of a trialing method for non-cancer pain will be made largely based on physician preference along with payer requirements. Most trials are performed in an outpatient setting with a single bolus intrathecal injection of a lipophilic opioid, such as fentanyl, and/or non-opioid, such as ziconotide. Alternatively, a continuous intrathecal or epidural infusion can be done, but this requires admission to a hospital and significantly adds to the cost and complexity of a trial. The advantage of epidural infusion is the simplicity of catheter placement and a much lower risk of post-dural puncture headache (PDPH). The development of a PDPH during trial may impair the patient's ability to determine the efficacy of the trial. An intrathecal catheter trial more closely mimics the permanent implant conditions and pharmacodynamics.[16] However, drug volume and concentration for a catheter trial may be substantially different from the conditions of an implanted infusion. An intrathecal bolus injection trial provides simplicity, reduced costs, and a low incidence of PDPH. However, it carries a significant risk of false-positive results. The PACC guidelines note that either bolus or catheter trials are acceptable.[27]

Trials for cancer pain can be performed in a similar fashion. However, the lack of prognostic evidence for trials calls into question their value in patients with rapidly progressive disease near the end of life. The PACC guidelines note that a trial is not required for patients with advanced cancer pain, and another consensus guide regarding intrathecal therapy for cancer pain noted that the risks associated with the trial and delay of therapy might not outweigh the alleged prognostic benefits.[5,27] However, other experts have recommended the use of a trial in cancer pain to give the patient and physician the opportunity to evaluate potential responses and possible side effects.[19]

Trials of intrathecal baclofen therapy for spasticity are considerably more straightforward than those for cancer and non-cancer pain. There are clear, objective outcome measures of spasticity that can be assessed to determine response. The commonly used criterion for a successful trial is a two-point reduction on the modified Ashworth scale for grading spasticity (Box 72.2).[49,50] Patients may also demonstrate improvements in joint range of motion.

The baclofen trial consists of a bolus intrathecal injection of 25–50 mcg of baclofen and is performed in an outpatient setting. The onset of effect occurs in 1–3 h and may last 6–8 h.[51] The patient is then evaluated with serial examinations to determine response. If the patient fails to respond, the trial may be repeated on a subsequent day at a higher dose.

Tolerance to intrathecal opioids develops over time, similar to systemically administered opioids. Therefore intrathecal dose escalation is common.[36,52,53] The PACC guidelines of both 2012 and 2016 include a maximum daily dose and concentration of intrathecal opioids and non-opioid analgesics. The 2016 guidelines added the recommendation to reevaluate doses of fentanyl that exceed 1000 mcg/day. Noting that high dose lipophilic opioid infusions may have limited additional efficacy and result in systemic concentrations similar to transdermal systemic delivery.[27]

Many patients being considered for intrathecal therapy to treat chronic pain are already receiving systemic opioids. Some studies have shown a total oral opioid dose reduction after implantation of IDDS. One retrospective study of insurance claims data found

• BOX 72.2 Modified Ashworth Scale for Spasticity

Ashworth Number	Description
0	No increase in muscle tone
1	Slight increase in tone manifested by a catch or minimal increased resistance at the end of ROM
1+	Slight increase in tone manifested by a catch followed by minimal resistance throughout the remainder of ROM
2	More marked increase in tone throughout ROM
3	Considerably increased tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

ROM, Range of motion.

(From Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67:206–207.)

that 43% of patients with chronic non-cancer pain who were on opioids before IDDS implant had discontinued all opioids one year after implant. Additionally, about three-fourths of those who failed to eliminate opioids saw a dose reduction in total oral morphine equivalents.[54] Regardless, both this and other studies show a significant portion of patients who remain on systemic opioids in addition to the intrathecal opioids.

There may be advantages to weaning the patient off systemic opioids prior to a trial. The PACC guidelines recommend reducing or eliminating systemic opioids prior to a trial or implantation of an IDDS.[27] A pre-trial drug holiday affords the opportunity to evaluate the patient and their pain without systemic opioids. This will also reduce tolerance, allowing for a better assessment of response to intrathecal therapy during the trial. The tapering process may uncover signs of opioid use disorder prior to proceeding with an implant. An addictionology consult should be considered for patients who cannot wean from opioids because of severe withdrawal symptoms.

Weaning patients off opioids prior to the implant may result in lower doses of intrathecal opioids. Evidence from small retrospective studies exists for the benefits of eliminating systemic opioids prior to an intrathecal trial.[55,56] These studies suggest that lower trial and IDDS starting doses can be achieved when systemic opioids are eliminated for several weeks prior to a trial. This approach has been referred to as micro-dosing because of the use of intrathecal morphine in the microgram dose range. Conversely, at least one study showed that lower systemic opioid doses at baseline did not protect against dose escalation after IDDS implantation.[57]

Consideration should be given for when and where to initiate intrathecal infusion after implantation. Compared to implantation of spinal cord stimulator devices, there is a significantly higher risk of mortality after implant or replacement of intrathecal pumps.[58] Initiating the infusion during an inpatient admission after pump implantation allows for close monitoring for adverse effects. When the pump implant is performed as an outpatient surgical procedure, more caution should be employed in initiating the infusion. The PACC guidelines recommend no more than one-half the trial dose as a starting daily infusion.[27] When starting drug infusion doses outside the PACC guideline starting dose range, it is recommended to initiate the infusion in an inpatient monitored setting.

Implantation

Location of Pump Placement

There are several considerations when choosing where to locate the pump. Patient comfort is of primary importance. To avoid rubbing, the pump must be located away from bony prominences, including the iliac crest and ribs. The amount of subcutaneous fat is also important. There may be too little space and tissue in the flank in the average-sized patient, whereas, in the morbidly obese patient, there may be too much subcutaneous fat in the abdomen. Have the patient sit up to mark the site to ensure that the pump will not lie below the beltline. Discuss the patient's sleeping habits to determine if the patient is a side sleeper. If so, then place the pump in the contralateral abdomen. In most cases, the most appropriate location for pump placement is in either the left or right lower quadrant of the abdomen.[59] Unlike spinal cord stimulator pulse generators, the size of intrathecal pumps may make placement in the flank or upper gluteal region uncomfortable for average-sized patients. Placement of the pump pocket in the abdomen necessitates positioning the patient in lateral decubitus for the surgical procedure. Proper attention to positioning is necessary to ensure that both the pump site and catheter insertion site are accessible without breaking scrub and repositioning.

Patients who have had multiple abdominal surgeries may pose a challenge in locating the pump pocket. If an abdominal site is impossible, a smaller 20 mL pump may be placed in the superior gluteal region. In larger patients, there may also be room to place the pump in the flank midway between the 12th rib and the iliac crest. A consultation with a plastic surgeon may be helpful in patients with limited implant site options.

When re-implanting a pump after a previous pump site infection, it may be useful to use a new location, such as the contralateral abdomen, to minimize re-infection risk. Placement of a pump into scar tissue is not recommended, as the blood supply can be erratic, limiting the delivery of antibiotics to the area during implantation. This is evident with pump re-implantations for battery failure in which the capsule surrounding the old pump has minimal bleeding when opened. In these cases, meticulous care must be taken with sterile technique to minimize the risk of infection with the re-implant. When replacing a pump using the existing pump pocket, it may be beneficial to excise the capsule prior to the implant of the new pump.

Anesthesia for Pump Implantation

Intrathecal pump implantation can be performed under local anesthesia with sedation, spinal anesthesia, or general anesthesia. The choice of anesthesia method will depend on physician preference and experience and patient comorbidities and comfort. One option is to place the intrathecal catheter percutaneously under local anesthesia followed by a spinal anesthetic for incision, catheter anchoring, tunneling, and creation of the pump pocket. If implanting under spinal anesthesia, the implanter will first place the Tuohy needle into the intrathecal space under local anesthesia. The implanter can then thread the intrathecal catheter through the Tuohy. Once the catheter is confirmed in the intrathecal space radiographically and by the free flow of cerebrospinal fluid (CSF), injection of 20–30 mg of preservative-free lidocaine will achieve adequate spinal anesthesia for both the posterior midline incision and abdominal pump pocket incision. The entire procedure can also be performed under local anesthesia with moderate sedation without the spinal anesthetic injection. These two methods allow for communication with the patient during catheter placement to minimize the risk of nerve injury.[41,59] Alternatively, general anesthesia may provide a more comfortable implant procedure for the patient or be preferred for patients with significant spasticity or in patients who would be unable to tolerate positioning and surgery under moderate sedation.[41]

Patient Positioning

Most commonly, the pump will be located in the abdomen, which necessitates either a lateral decubitus position or repositioning the patient from prone to supine midway through the surgery. Most implanters use the lateral decubitus position to avoid the time delay and potential infection risk of repositioning. Be sure to place the patient with the side of the planned pump pocket facing up. Careful positioning with pressure points padded and an axillary roll in place is necessary for patient comfort and to avoid intraoperative nerve compression injuries. The use of sticky rolls or bean bags to support the upper abdomen or posterior thorax

may assist in positioning the patient to hold them in the lateral decubitus position. Taking the time to ensure the patient is well supported and the sagittal axis is perpendicular to the operating room table will ensure a true anterior-posterior view with fluoroscopy. Position the patient's arms to avoid interfering with fluoroscopic visualization. As stated before, it is critical to mark the pump implantation site with the patient in the sitting position because the tissue will shift when in the lateral position. Marking the patient while in the lateral position risks having the pump end up in an uncomfortable location.

Surgical Technique

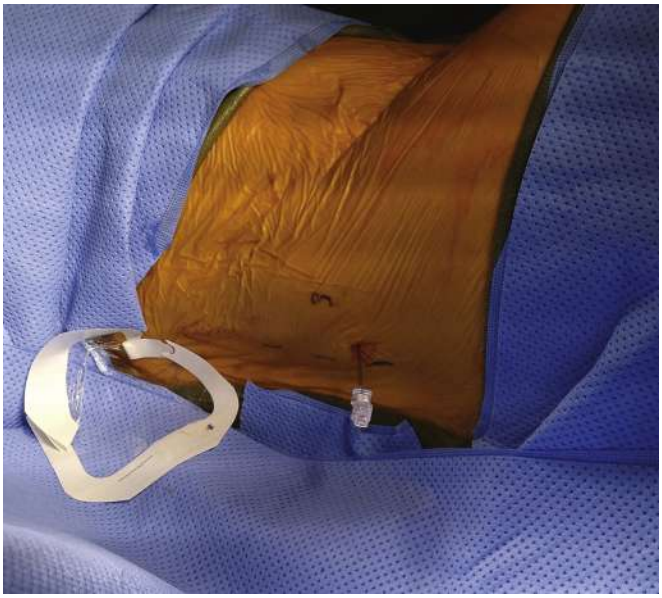
Sterile Technique

Good sterile technique and preoperative antibiotics are the two most important controllable factors in preventing wound infections. In a study of primary implantations and revisions of intrathecal baclofen pumps in pediatric and adult patients, an infection rate of 4%–5% was found.[60] In more than half of the infections, the primary organism was *Staphylococcus aureus*. In a multi-center prospective study of intrathecal pump implantations for both pain and spasticity, Follett found that the most common complication was an infection, with an incidence of 7%.[61] Most surgical site infections in clean surgeries are because of skin microorganisms.[62,64] Careful cleansing of both the surgeon's hands and the patient's skin at the operative site with either a *chlorhexidine-alcohol* or povidone-iodine scrub reduces skin bacterial counts. Scrubs of 2–3 min are superior to shorter scrub times. Several studies have suggested that chlorhexidine-alcohol scrubs may be superior to povidone-iodine scrubs.[64] Body hair should be removed if excessive, and removal should be performed with clippers instead of shaving. Shaving results in microtrauma of the skin, resulting in the inability of the antiseptics to reach the cracks and crevices that may be hiding bacteria.[62,41] Use of chlorhexidine skin preparation of the surgical site followed by the use of povidone-iodine-impregnated adhesive skin drapes is recommended, as this produces another barrier between the skin flora and wound.[41] If using these drapes, allow extra time for the skin prep to dry so that the adhesive will stick firmly to the skin. Adherence to the patient's skin is necessary for the antiseptic effect. Surgeons and assistants should double glove to reduce the infection risk associated with glove puncture.[41] Prophylactic systemic antibiotics against the most likely pathogens (skin flora) should be administered within 60 min of skin incision. Current guidelines for neurosurgical procedures are for cefazolin 2 g (3 g for adults >120 kg). If the patient has an allergy to cephalosporins, the recommended alternatives are clindamycin or vancomycin.[64] There is no evidence supporting the postoperative administration of oral antibiotics to prevent wound infections.[41]

Additional practices that may reduce the risk of infection include (1) limiting operative time, (2) limiting tissue trauma and maintaining hemostasis, (3) irrigating the incisions with saline prior to closure, and (4) re-gloving after surgical dissection is complete and before handling the pump. These practices may reduce the risk of surgical site infections.[41]

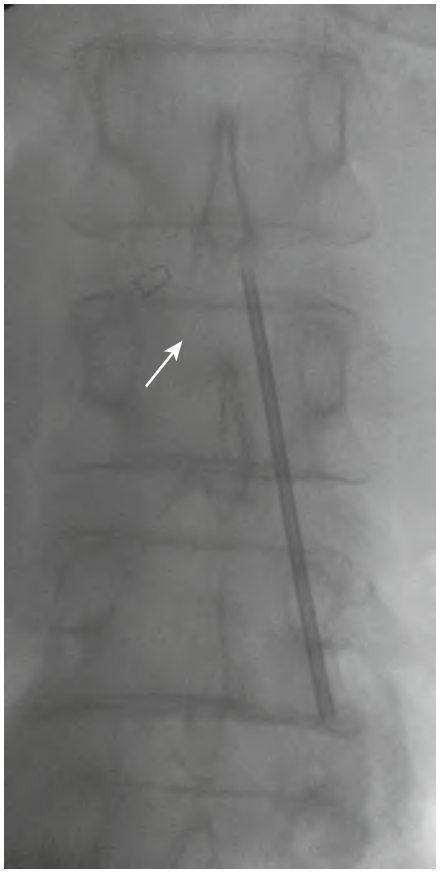
Posterior Incision, Catheter Placement, and Anchoring

If performing the implant under spinal anesthesia, the Tuohy needle will be placed percutaneously before making an incision. If using local/sedation or general anesthesia for the implant, most implanters will assess the needle entry then make an incision down to paravertebral fascia before placing the Tuohy. In either case, the spinous processes on either side of the planned intervertebral space for needle insertion should be marked on the skin. This will identify the midline incision to be used for dissection and anchoring. Next, mark a location for needle insertion to achieve a shallow-angle, paramedian oblique placement (Fig. 72.5). An angle of approximately 30 degrees off of the spine is ideal.[8] An insertion angle that is too steep will make it more difficult to thread the catheter. For an average-sized patient, the skin entry point will be 1–2 cm lateral to the midline on the side of the intended pump pocket and 1–1.5 vertebral levels caudad to the targeted interlaminar entry site. The typical entry site will range from the L2–L4 interlaminar spaces unless anatomic considerations or previous surgery dictates otherwise. When making an incision prior to needle placement, the incision should be approximately one-third above the needle entry into the fascia and two-thirds below the needle entry site.



• **Figure 72.5** Paramedian needle insertion, same side as the abdominal pump pocket.

With the stylet in place, the introducer needle should be advanced to the superior edge of the caudad lamina for the target space. After touching the lamina to gauge depth, the needle is then walked off the edge to the midline of the interlaminar space (Fig. 72.6). It is best to walk off the lamina just lateral to the midline. Further advancement into the intrathecal space will then be more midline. Next, rotate the bevel of the needle 90 degrees toward the midline so that the needle bevel will be parallel to the longitudinal fibers of the dura. This will spread rather than cut the fibers to reduce the chance of PDPH. The fluoroscopic view should then be rotated to a lateral view to monitor the needle depth as it is advanced into the intrathecal space. With gentle aspiration, the needle is advanced until there is a return of CSF. If there is no return of CSF despite adequate depth on lateral fluoroscopic view, rotate the needle back 90 degrees to the original position, which may result in CSF return. If there is no CSF return, rotate 90 degrees and gently advance the needle. Once the intrathecal space has been accessed, replace the needle stylet to stop CSF flow until ready to place the catheter. Turn the bevel tip cephalad. Ensure that the catheter guidewire is fully advanced into the catheter and is in place during the insertion and positioning of the catheter. Advance the catheter through the introducer to the desired level under fluoroscopic guidance (Fig. 72.7). Once



• **Figure 72.6** Needle advanced into the epidural space after walking off the superior edge of the L3 lamina. The *white arrow* indicates the edge of the lamina.

• **Figure 72.7** Lateral image with the needle (*white arrow*) in the intrathecal space and the catheter tip visible five vertebral levels above the entry site (*black arrow*).

the catheter tip is beyond the distal portion of the needle, extreme caution should be used should the catheter need to be withdrawn, as catheter shearing or damage may occur. If there is the slightest resistance when attempting to withdraw the catheter through the needle, it is recommended that the needle and catheter be removed together and the process restarted with needle placement.

If using the percutaneous needle placement technique, leave the needle in place to protect the catheter and make an incision in the midline over the spinous processes medial to the needle entry site down to the supraspinous ligament. The incision must be large enough to create a pocket for anchor placement, approximately 5 cm. Undermine the edges of the incision laterally along the fascial plane to create space for anchor placement and fully expose the traversing introducer needle (Fig. 72.8).

If the needle was placed percutaneously or within an incision, carefully withdraw the needle over the catheter with the catheter guidewire. To prevent inadvertent withdrawal of the catheter, hold the catheter steady, just distal to where it enters into the needle as the needle is withdrawn. Once the needle is removed, hold the catheter firmly at the entry site into the fascia at the level of the supraspinous ligament, and withdraw the guidewire. Recheck the catheter position under fluoroscopy to ensure proper placement (Fig. 72.9). Injection of a small amount of contrast may help to make the catheter visible under fluoroscopy.

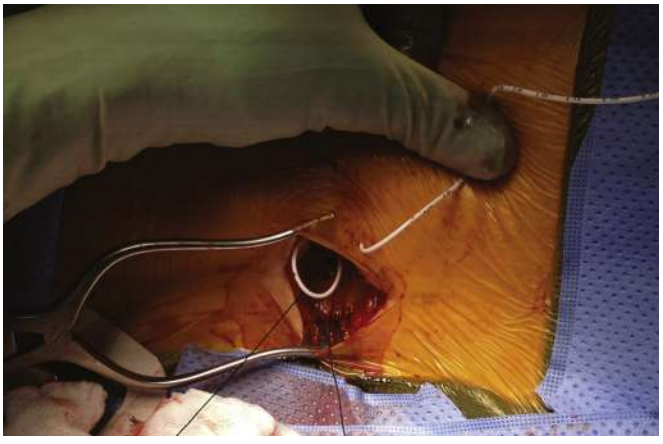
If using the percutaneous needle technique, continue holding the catheter at the fascia and bring the external portion of the catheter through the skin into the posterior pocket (Fig. 72.10).

• **Figure 72.8** Posterior incision medial to needle insertion down to the supraspinous ligament. Pocket undermined laterally to expose the needle within the pocket.

Clamp the end of the catheter with a rubber shod-covered clamp to prevent CSF loss while anchoring and tunneling.

Using a nonabsorbable suture, tie a purse-string suture through the fascia around the catheter to prevent CSF leak tracking back along the catheter.[11] Next, thread the catheter through the anchor deploy device and seat the anchor tip into the fascia. Hold the anchor with forceps and deploy the anchor. Place a 0–0 silk suture thru each anchor islet into the fascia and tie down tight. An additional 0–0 silk suture is then tied around the neck of the anchor, making sure the suture fits in the groove on the anchor.

• **Figure 72.9** Confirm catheter tip (*white arrow*) location on the fluoroscopic image prior to anchoring.



• **Figure 72.10** After carefully removing the needle and guidewire, bring the external section of the catheter into the pocket.

This will ensure a tight fit to hold the catheter. Ensure the anchor is attached firmly to the fascia and not to subcutaneous fat and that the distal tip of the anchor is buried into the fascia. Catheter migration out of the intrathecal space may occur if the anchor is not firmly attached to the fascia or if there is an extra catheter between the anchor and fascial entry point.

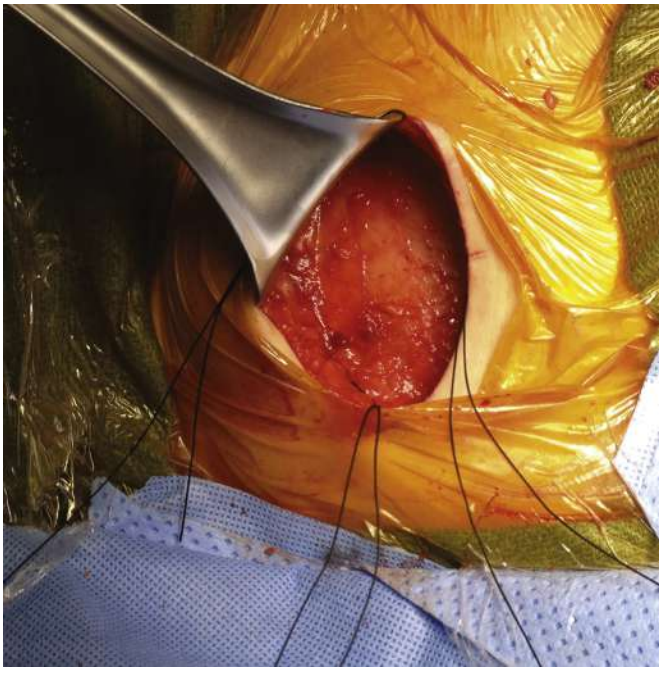
Pump Pocket

Once the catheter is securely anchored, the implanter can turn attention to creating a subcutaneous pocket for the pump. If performing the implant under sedation with local anesthesia, infiltrate a copious amount of local anesthetic around the planned pump pocket incision. At the abdominal site previously marked, make an incision down through the scarpa's fascia to subcutaneous fat. Obtain hemostasis with electrocautery as necessary and extend the incision to a depth of at least 1.5 cm but no more than 2.5 cm. Using careful dissection, undermine along a horizontal plane to create a pocket that just fits the pump. An oversized pocket increases the risk of seroma and shifting or flipping of the pump. The pocket should be undermined predominantly cephalad or caudad to the incision so that the final incision does not lie directly over the refill port of the pump. Accessing the refill port is much easier if the incision scar is not directly over the port. After ensuring proper fit of the pump, place 0-0 silk sutures into at least three corners of the pocket for anchoring the pump (Fig. 72.11). These sutures should be firmly anchored to the fascia. Failure to adequately anchor the pump at three or more sites may result in the pump flipping inside the pocket.

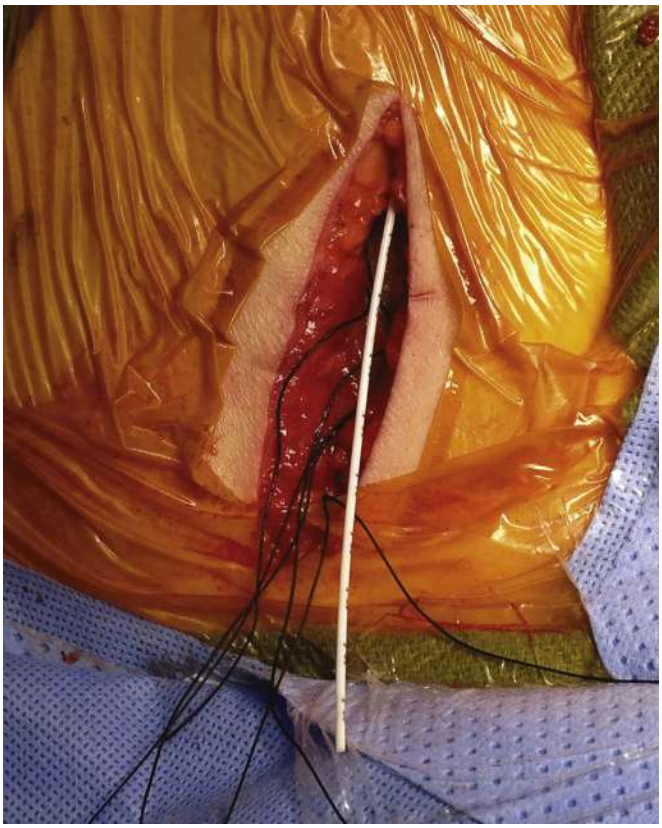
Tunneling

Once the pocket is prepared, the catheter must be tunneled from the posterior incision to the pump pocket (Fig. 72.12). The supplied tunneling device may be bent in a gentle curve to facilitate passage subcutaneously from the posterior incision to the pump pocket incision. Start inside the posterior pocket with pressure and a gentle twisting motion to begin passing the tunneling device toward the pump pocket. Place one hand on the skin surface over the tunneling device tip. The tip should be palpable without piercing the skin throughout the course to ensure it is neither too deep nor too superficial. Once the introducer has entered the pump pocket, remove the handle and begin passing the catheter through the introducer toward the pocket. Remove the introducer from the pump pocket side. Excess catheter length will be coiled beneath the pump.[8] Once the catheter has been tunneled, irrigate each pocket with copious amounts of normal saline.

Ensure patency of the catheter by observing CSF flow from the tip. Attach the catheter to the provided catheter connector. The



• **Figure 72.11** Sutures placed in three corners to tie down the pump through the attached suture rings.



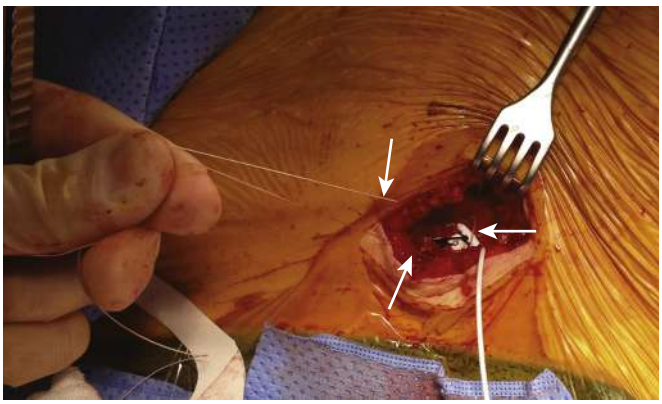
• **Figure 72.12** The catheter is tunneled into the pump pocket using the provided tunneling device.

• **Figure 72.13** Pump tightly in place within the pocket with the access port facing out.

connector is then attached to the pump. Ensure that it is firmly connected to the pump. Access the side port using the provided side port access needle and gently aspirate to make sure there is a flow of CSF. Insert the pump into its pocket and use the previously placed zero silk sutures to tie it down in three of the corner suture loops. Make sure the catheter is not entangled in these sutures to avoid kinking. Place coils of excess catheter behind the pump and ensure that the pump refill port is facing up (Fig. 72.13).[8]

Closure

Before closure of the posterior pocket, pass one 2-0 Vicryl suture through the dorsolumbar fascia alongside the anchor, then cross the suture over the anchor and through the fascia on the opposite side (Fig. 72.14). Pull the two sides together to tightly cover the anchor site and tie down (Fig. 72.15). This tight pocket over the anchor will help prevent catheter migration out of the intrathecal space. For deep incisions, the deep fascia may need to be closed using interrupted inverted absorbable sutures. For shallower incisions, only the subcutaneous fascia will need to be closed, using interrupted inverted sutures with the spacing close enough that a fingertip placed between sutures is unable to pass below the fascia into the incision. For the pump site, only the subcutaneous fascia will require closure, using interrupted inverted absorbable sutures similar to the posterior incision closure technique. Skin closure of both incisions may be performed with a running subcuticular closure of 3–0 Monocryl, Dermabond, and steri-strips or with staples. Last, place dressings over the incisions. Placement of an abdominal binder, with instructions to wear it for two weeks postoperatively, may decrease the incidence of seroma formation in the pump pocket.[41]



• **Figure 72.14** One suture was placed through the dorsolumbar fascia on one side of the anchor then crossed over to the other side *(arrows)* to close a flap of tissue over the top of the anchor. This will help prevent the migration of the catheter out of the intrathecal space.

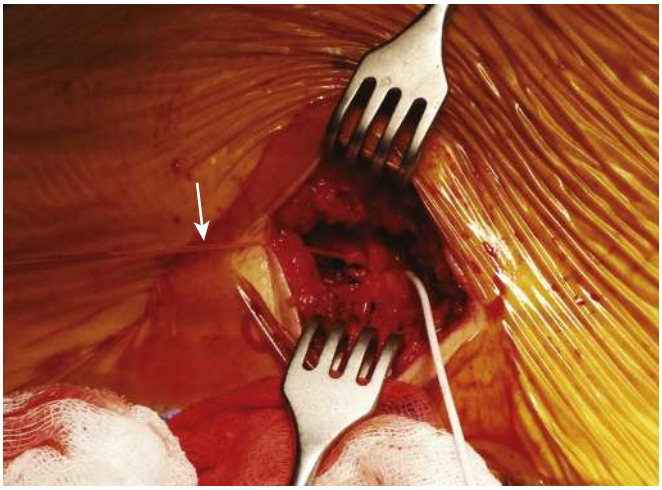
Complications

Perioperative Complications

The implantation of an IDDS exposes the patient to risks similar to those of other surgical or invasive procedures, such as bleeding, infection, wound dehiscence, and neurologic injury. In addition, there is a risk of CSF leakage with PDPH, migration of the intrathecal catheter, and pump site complications, such as seroma formation.

Bleeding

Intraoperative bleeding is most likely problematic in patients with a history of bleeding diathesis or hepatic disease or those on anticoagulant therapy. Patients with suspected coagulation disorders should be evaluated carefully prior to implantation. A multi-society group



• **Figure 72.15** Suture pulled tight (*white arrow*) to close a flap over the top of the anchor.

has developed guidelines regarding the management of anticoagulants for chronic pain conditions (Box 72.1). As noted earlier, these guidelines divide chronic pain procedures into three risk strata: low, intermediate, and high. The implantation of an intrathecal pump is categorized as a high-risk procedure. These guidelines should be followed to reduce the risk of potentially catastrophic spinal or epidural hematoma formation.[44]

Infection

The incidence of infection following intrathecal pump implantation has been reported to be between 2.5% and 9%.[42] Most infections occur at the pump pocket site and are present within 15–45 days after implantation. Pediatric patients implanted for treatment of spasticity have been found to have slightly higher rates of post-implantation infections.[60] In addition to local infection at the pump site, there is a risk of infection spreading to the CSF with resulting meningitis. This risk necessitates good infection control practices to prevent surgical site infections and carefully evaluate any suspected infection (discussed previously). In most cases, a pump pocket infection will require explanting both the device and the catheter.

The clinical presentation of a local pump pocket infection may include increased pain, fever, erythema, tenderness, swelling, purulent drainage, and warmth at the pump site. In the case of CSF infection and meningitis, the patient may present with nuchal rigidity, headache, nausea, vomiting, and fever. In either case, the patient may have an elevated white blood count (WBC), C-reactive protein, or erythrocyte sedimentation rate. The formation of a seroma within the pump pocket may mimic a local infection with swelling and erythema. Percutaneous drainage and culture of fluid may assist in making the diagnosis. The most common pathogens implicated are Staphalococcus.[42]

If an infection is suspected, the pump and catheter should be removed immediately. Antibiotics should not be administered until the pump is removed and wound cultures are obtained. Antibiotics administered before cultures are obtained can make it difficult to identify the bacteria, thus committing the patient to a longer course of broad coverage antibiotic therapy.

Cerebrospinal Fluid Leaks

CSF leaks may occur around the catheter via the dural puncture site or because of disconnection, fracture, or puncture of the catheter. The leakage of CSF may result in a PDPH. Generally, CSF leaks that are not because of catheter fracture or disconnection are self-limiting and may be treated conservatively. However, if the leak and symptoms persist, an epidural blood patch may be performed under fluoroscopic guidance to avoid damage to the catheter.[6,63]

Severe CSF leaks may result in CSF fluid collections in the posterior catheter site pocket. These can be difficult to treat, and if an epidural blood patch does not resolve the leak, injection of 1 mL of fibrin glue at the dural entry site under fluoroscopy can be considered. If this does not resolve the leak, explant of the system may be necessary.

Persistent or recurrent fluid collection in the pump pocket after percutaneous drainage should raise the suspicion of a catheter disconnect from the pump with a CSF leak into the pump pocket. Percutaneous side port access with an injection of contrast under fluoroscopy can diagnose this complication.

Catheter Complications

Catheter-related problems are the most common complications following the implantation of IDDSs. Although the reported occurrence varies, Follet and Naumann found a rate of 18.6% in a prospective study of catheter-related complications.[65] These problems include fracture, puncture, disconnection, migration, or dislodgement from the intrathecal space. Among these, catheter migration is the most common and usually results from improper anchoring of the catheter to the fascia.[65] Catheter failures may present as inadequate analgesia, CSF leaks, or withdrawal symptoms. Evaluation of catheter complications starts with accessing the side port. If CSF can be aspirated freely, then a fluoroscopic evaluation with an injection of contrast may help identify leaks and the location of the catheter within the intrathecal space. If CSF cannot be aspirated, one must fill the pump with saline and clear the catheter of the drug before injecting contrast to avoid bolus injection of drug intrathecally. Contrast studies may not detect small leaks, kinks, or breakage. A computed tomography (CT) myelogram following injection of iodinated contrast through the side port may be required to identify the location of a leak or the formation of a granuloma at the catheter tip. Gadolinium based contrast agent should not be used because of probable occurrence of encephalopathy or death from intrathecal gadolinium injection.[67–69]

Granuloma Formation

Granulomas are aseptic inflammatory masses composed of macrophages, neutrophils, and monocytes with granulation tissue.[4,65,66] The formation of a granuloma at the catheter tip may cause a loss of analgesic efficacy, progressive neurologic symptoms resulting from a mass effect on the spinal cord, and permanent neurologic injury. In a study of granulomas reported to the manufacturer of one pump system, the authors calculated an incidence of 0.49% of implanted systems.[66] Because many granulomas go undetected or unreported, the actual incidence is likely much higher. The most commonly reported symptoms are decreased efficacy of analgesia and pain. Neurologic symptoms reported include weakness, numbness, and incontinence.[4] Risk factors for granuloma formation include a high dose and high concentration infusion of opioids.[4,41,66] The most commonly implicated drug has been morphine, but other opioids and, rarely, baclofen have been associated with granuloma formation. Ziconotide has not been associated with granuloma formation.[4,41] Imaging by MRI with contrast or CT myelogram can aid in the evaluation of a suspected granuloma. However, in the authors' experience, CT myelogram is superior, as catheter identification can be difficult with MRI, and

we have seen two cases where MRI with contrast failed to demonstrate a granuloma, whereas subsequent CT myelogram diagnosed the granuloma. The treatment employed will depend on the presence and severity of any neurologic symptoms. Options include replacement of the intrathecal infusate with saline, removal of the catheter, or surgical exploration and mass resection.[4]

II Intrathecal Medications

There are currently only three FDA approved medications for use in IDDSs: morphine, baclofen, and ziconotide. Several medications are commonly used without FDA approval, and others less commonly used that are considered investigational.

This section will focus on FDA approved medications with a brief overview of commonly used off-label medications.

Opioids (Box 72.3)

Opioid analgesics exert their actions through the inhibition of target cell activity. Whereas peripherally located opioid receptors have been identified, the predominant analgesic sites are believed to reside in the central nervous system (CNS). In the brain, these receptor sites include the brainstem, thalamus, forebrain, and mesencephalon. In the spinal cord, they include the postsynaptic receptors located on cells originating in the dorsal horn and presynaptic receptors found on the spinal terminals of primary afferent fibers.[70]

The effects of opioids are determined by their affinity for endogenous receptors and their ability to reach those receptors. The onset of analgesia is similar for intrathecal and epidural opioids, suggesting that the penetration of neural tissue—and not the meninges—is the rate-limiting step.

Lipid solubility determines, in part, many important characteristics of intrathecal opioids, including the spread of analgesia and side effects. Highly water-soluble opioids, such as morphine, exhibit a greater degree of rostral spread when injected into the subarachnoid or epidural space than lipid-soluble compounds so that in pain conditions requiring higher spinal levels or more extensive coverage, the degree of analgesia they confer may be superior. Conversely, since many of the adverse effects of spinal opioids, such as nausea and vomiting and delayed respiratory depression, result from interaction with opioid receptors in the brain, the more water-soluble compounds are associated with a higher incidence of these problems.

Whereas the earliest studies evaluating the chronic use of intrathecal opioids were conducted in patients suffering from cancer pain, other studies have found intrathecal and epidural narcotics to be effective in non-malignant pain as well.[71–72] These conditions include not only nociceptive pain but also neuropathic pain, a heterogeneous group of disorders originally believed to be resistant to narcotics. Certain aspects of neuropathic pain, such as tactile allodynia, may be less responsive to the effects of spinal opioids. Therefore many neuropathic conditions require adding non-opioid analgesics to spinal opioids for successful pain relief.[73–75] The caveat with the treatment of non-malignant pain via intrathecal opioids is that these patients have a higher likelihood of complications resulting from opioid therapy because of their traditional life expectancy than those with cancer. Aside from the common intrathecal opioid side effects such as tolerance, constipation, sweating, nausea, and urinary retention, these patients are at risk for the development of intrathecal granulomas. Factors that are positively associated with the development of catheter tip granuloma include drug dosage, drug concentration, and the duration of intrathecal opioid therapy. In 2017, the PACC guidelines published recommendations for the maximum daily dose and maximum concentration of intrathecal medications (see section I).

When opioids are administered directly into the CSF, only a fraction of the systemic dose is required, as there are no anatomic barriers to be crossed, and vascular reuptake is slow. Not all side effects of intrathecal opioids are dose-related, but in many instances, the drastic reduction in dosage translates into reduced side effects. Among the adverse opioid effects reduced by switching from oral formulations to spinal administration are sedation and constipation. Effects that may be increased include pruritus, urinary retention, and edema. The mechanisms contributing to the various adverse effects of opioids are incompletely understood but probably multifactorial and include those mediated via interaction with specific opioid receptors and those that are not. Undesirable effects not mediated by opioid receptors, such as CNS excitation and hyperalgesia, cannot be reversed with naloxone. The incidence of various opioid-induced side effects depends on a number of different factors, including the opioid infused, route of administration and dosage, the extent of disease, concurrent drug (e.g. oral opioids, adjuvants), age, concomitant medical problems, and prior exposure to opioids. The most frequent side effects of intrathecal morphine are constipation, sweating, urinary retention, nausea and vomiting, and disturbances of the libido.[76–77]

• BOX 72.3 Intrathecal Opioid Medications and Dosing

		Maximum 24 h dose	Maximum Concentration
FDA approved:	Morphine	15 mg	20 mg/mL
Common Use:	Hydromorphone		
	Fentanyl	10 mg	15 mg/mL
	Sufentanil	1000 mcg	10 mg/mL
		500 mcg	5 mg/mL

Calcium Channel Antagonists (Box 72.4)

Voltage-dependent calcium channel (VDCC) conduction plays an integral role in pain transmission. The neuraxial administration of some VDCC modulators has been shown to produce antinociception, anti-allodynia, and anti-hyperalgesia in animals. High threshold VDCCs, including N- and P/Q channels, are primarily found at synaptic sites involved in the release of transmitters; L-type channels are mainly observed at cell bodies and dendrites.[78–79] Several VDCCs have been found to co-localize in the same neuron. Therefore antagonists to a given channel type usually

• BOX 72.4 Intrathecal Calcium Channel Medications

		Maximum 24 h dose	Maximum concentration
FDA approved:	Ziconotide	19.2 mcg	100 mcg/mL
Common use:	None		

block only a fraction of the VDCCs present, and hence may have additive effects when combined. Finally, the relative importance of the various channel types depends on the functional status of the neuron. For instance, in acute models of nociception in uninjured naive animals, there is a large body of evidence implicating N-types, limited evidence for L-types, and no evidence for P/Q types in producing antinociception. However, under conditions of persistent nociception induced in animals by chemical, inflammatory, or neuropathic stimuli, all three of these subtypes have been found to have anti-allodynic or anti-hyperalgesic properties.[80–81]

Ziconotide is a synthetic form of the peptide, ω-Conotoxin MVIIA, isolated from the venom of the marine cone snail, Conus magus.[82] It potently blocks N-type VDCCs *in vitro* and inhibits wind-up. The process of wind-up involves the activation of spinal NMDA receptors after injury, which induces a state of facilitated processing from repetitive small afferent fiber stimulation. This leads to an increased response to high and low threshold stimulation and enhanced receptor field size. Ziconotide is the first member in the new drug class of selective N-type voltage-sensitive calcium channel blockers. Ziconotide blocks N-type calcium channels in the spinal cord and inhibits the release of pain neurotransmitters from the central terminals of primary afferent neurons. By way of this mechanism, ziconotide has been found to effectively reduce pain. In a multi-center, double-blind, placebo controlled study evaluating intrathecal ziconotide for the treatment of refractory pain in 111 patients with cancer and AIDS, Staats et al. found that the treatment group obtained significantly enhanced pain relief than the control group (53% vs. 18% improvement).[83] The observation that there was no loss of efficacy for ziconotide in the maintenance phase is consistent with animal studies showing the absence of tolerance with calcium channel blockers. The most common side effects noted in this study were confusion, somnolence, and urinary retention. However, 97% of patients receiving ziconotide experience side effects, and 30% had serious adverse events. All side effects were reversible, with their incidence decreasing after the initial dosing period. In a randomized double-blind, placebo controlled trial, Wallace et al. demonstrated that IT ziconotide provides relief in patients suffering from severe chronic non-malignant pain who are unresponsive to conventional therapy.[84] Patients were treated over six days and were found to respond to dosing of 0.1–2.4 μg/h. The original starting dose of 0.4 μg/h was decreased because of a high incidence of side effects. The mean reduction in pain score from baseline was 31.2% in the treatment group compared to 6.0% in the placebo group. Patients in the treatment group reported suffering more side effects, including abnormal gait, amblyopia, dizziness, nausea, nystagmus, pain, urinary retention, and vomiting. However, Rauck et al. demonstrated that slow titration could provide comparable pain relief while minimizing the side effects experienced by patients.[85] Wallace et al. showed that ziconotide could be safely given for the long-term treatment of refractory pain.[86] Over 644 patients with severe chronic pain participated in this open-label, multi-center longer-term trial. Thirty-two percent of patients receiving ziconotide for over 360 days, with a dose range between 0.048 μg/day and 240 μg/day, experienced greater than or equal to 32.7% improvement in pain scores. Although only FDA approved as a single therapy, evidence suggests that ziconotide can be safely combined when administered intrathecally with baclofen, morphine, sufentanil, and bupivacaine.[87–89] Webster et al. added morphine to stable IT ziconotide therapy in 25 patients, which resulted in a mean 26.3% reduction in pain and a 49.1% reduction in opioid consumption at week four of treatment. This study suggests a synergism between morphine and ziconotide.[90] When IT ziconotide is combined with other drugs such as opioids and baclofen, the stability declines, which may necessitate more frequent refills.[91]

The main limitations regarding the use of IT ziconotide are its steep cost and the high incidence (> 80% in many studies) of side effects, which can include the neurologic, psychiatric, cardiovascular, gastrointestinal, and genitourinary systems. Although ziconotide is now considered the first line treatment for chronic pain in some guidelines, this therapy has an extremely narrow therapeutic window with substantial side effects and should be reserved for patients in which other agents and therapies have been exhausted.

γ-Aminobutyric Acid Agonists (Box 72.5)

Three types of γ-aminobutyric acid (GABA) receptors are currently recognized: $GABA_A$, $GABA_B$, and $GABA_C$. Only $GABA_A$ and $GABA_B$ receptors are present in significant quantities within the CNS. The $GABA_A$ receptor is a ligand-gated ion channel. Activation of this receptor by GABA results in an influx of chloride ions and stabilization of the membrane potential, which decreases neuronal excitability. The receptor possesses two binding sites for GABA and sites at which barbiturates, inhalational anesthetics, neurosteroids, and benzodiazepines bind to modulate the action of GABA. The receptor itself is a pentameric arrangement of different subunits. In contrast, the $GABA_B$ receptor is a metabotropic receptor. Activation of the $GABA_B$ receptor by GABA results in activation of inwardly rectifying potassium channels, inhibition of calcium channels, and/or inhibition of adenylate cyclase activity, all of which suppress neuronal excitability.

In laboratory animals, $GABA_A$ agonists, including muscimol, isoguvacine, and midazolam, have anti-allodynic and anti-hyperalgesic effects in chronic pain models, while the $GABA_A$ antagonists, bicuculline and picrotoxin, induce allodynia and hyperalgesia in naive rats. However, $GABA_A$ receptors are also closely linked to large-diameter afferents and thus are likely involved in modulating innocuous sensations as well. Similar to $GABA_A$ receptors, $GABA_B$ receptors are found in the greatest abundance in the superficial dorsal horn of the spinal cord. Within the GABAergic system, nociceptive transmission is primarily regulated by $GABA_B$ receptor activity. The $GABA_B$ receptor agonist, baclofen, blocks the activity of peripheral C and A-delta nociceptive fibers. Further, in the spinal cord, $GABA_B$ receptors are found on interneurons and terminals from primary afferent neurons. $GABA_B$ receptor agonists administered via the intrathecal or epidural route produce pre- and postsynaptic inhibition and therefore block the release of glutamate, substance P, and calcitonin gene-related peptide from primary afferents and GABA from interneurons.

In human studies, both $GABA_A$ and $GABA_B$ agonists have been shown to contain analgesic effects when injected into the intrathecal or epidural space. The literature shows that the neuraxial administration of $GABA_A$ agonists combined with local anesthetics

• BOX 72.5 Intrathecal GABAergic Medications

FDA approved:	Baclofen	Maximum 24 h dose	Maximum concentration
		2 mg	4 mg/mL
Common use:	None		

increases the duration of motor and sensory block, increases the time to first analgesic request, and decreases postoperative analgesic requirements. The administration of the $GABA_A$ agonist, midazolam, via either the intrathecal or the epidural route in combination with a mixture of other analgesics, including local anesthetics and opioids, was found to reduce opioid requirements and enhance postoperative analgesia for a variety of different surgical procedures.[92–96] Many other studies have reported the efficacy of intrathecal midazolam for various pain conditions. However, the safety of its neuraxial use is controversial. Numerous animal studies have shown evidence of neurotoxicity with intrathecal midazolam, and it is considered a fifth-line neuraxial treatment for chronic pain.

Numerous studies support the use of neuraxial baclofen for spasticity in humans, and it is the only FDA approved intrathecal agent for the treatment of refractory spasticity. Multiple uncontrolled studies show intrathecal baclofen to be effective for some central pain conditions and a variety of conditions with spasticity, including stroke, phantom limb pain, spinal cord injury, cerebral palsy, amyotrophic lateral sclerosis, and multiple sclerosis.[97–100] Intrathecal baclofen has also been found to be an effective treatment for peripheral neuropathic pain conditions, such as complex regional pain syndrome.[101–103] In a small study by Lind et al., the authors found that the addition of intrathecal baclofen in patients treated with spinal cord stimulation for neuropathic pain improved pain scores to a greater degree than concomitant treatment with oral baclofen.[104] The beneficial effect of intrathecal baclofen was dose-dependent, peaking at 50 μg. Furthermore, at follow up, Lind et al. found that patients treated for a mean of 67 months enjoyed the same degree of pain relief, requiring only a modest (30%) dose increase.[105] Van Rijn et al. found that intrathecal baclofen provides substantial improvement in patients with dystonia and those with CRPS.[106] Thirty-six patients received a pump for continuous intrathecal baclofen for 12 months. Patients experienced a decrease in pain and disability and an improved quality of life. However, patients did experience a high complication rate, most often associated with pump or catheter system defects. Neuraxial baclofen has also been found to be beneficial in the treatment of musculoskeletal pain. Loubser and Akman found that intrathecal baclofen reduced musculoskeletal but not neurogenic pain in 12 patients with chronic spinal cord injury-related pain.[107] Based on the results of this study and the temporal disparity regarding its analgesic effects on central pain and muscle spasm, it is likely that different pain-relieving mechanisms exist for these two conditions.

At therapeutic doses, baclofen is associated with numerous adverse effects, including drowsiness, flaccidity, headache, confusion, hypotension, weight gain, constipation, nausea, urinary frequency, and sexual dysfunction.[108,109] Intrathecal baclofen overdose can lead to respiratory depression, seizures, obtundation, and, if not adequately treated, death. Withdrawal from the abrupt cessation of intrathecal baclofen treatment can last days to weeks, or possibly longer, and can also be life-threatening.[110,111] There is evidence to suggest that replacement with oral baclofen may not always be adequate to control the symptoms, possibly because oral baclofen does not reach the central concentrations near the range achieved with intrathecal administration.[110,112] Baclofen is currently considered a fourth line treatment for chronic pain.

Local Anesthetics

Although not FDA approved for continuous IT use, bupivacaine is the most common local anesthetic used off-label in IT therapy and has a long track record of safety and efficacy alone or in combination with morphine.

Bupivacaine is an amide local anesthetic with high lipid solubility with several properties that make it ideal for chronic intrathecal delivery. [113] Bupivacaine has motor sparing properties minimizing motor weakness at doses up to 15 mg/day. [114,115] Catheter tip location, CSF flow dynamics, and patient mobility may influence sensorimotor loss.[116] For example, a catheter that shifts onto a nerve root may result in motor weakness with higher bupivacaine concentrations and bolus dosing. Although tachyphylaxis has been reported at extremely high dose, there is an absence of tachyphylaxis at the most commonly used doses of up to 20 mg/day.[117,118] The most recent PACC guidelines recommend a starting dose of bupivacaine of 1–4 mg/day with titration up to a maximum dose of 10 mg/day (maximum concentration of 30 mg/mL), which is consistent with published studies of intrathecal bupivacaine for chronic pain.[116] Although there is conflicting literature, bupivacaine appears to have opioid sparing effects when combined with an opioid. A retrospective study in 109 subjects with an intrathecal opioid/bupivacaine combination showed improved pain control and a reduction in oral opioid use,[119] and another larger study in non-cancer pain showed a blunting of the opioid escalation.[114] A small double-blind randomized prospective study suggested that the addition of bupivacaine (up to 8 mg/day) to morphine or hydromorphone in post-laminectomy pain patients did not improve pain control.[120]

Although bupivacaine has a long track record for safety with chronic infusion for pain management, there have been animal study reports of toxicity, including spinal cord vacuolation in a rodent model[121] and minor leptomeningeal infiltration in a dog model.[122] Postmortem analysis of cancer patients who received chronic bupivacaine infusion did not show any pathologic conditions of the spinal cord.[123,124]

Adrenergic Agonists (Box 72.6)

Adrenergic agonists have analgesic effects when applied for the management of chronic pain. α-Adrenergic receptors are widely distributed throughout the body and comprise two clinically significant classes: α_1 and α_2. α_1 Receptors are found in the smooth muscle cells of the peripheral vasculature and play an essential role in the regulation of systemic vascular resistance[125]; they have no known significant role in analgesia. However, α_2 receptors are present throughout the peripheral and CNS and play a substantial role in modulating pain signals. There are several known subunits of the α-receptor: 2a, 2b, and 2c. Clonidine binds to pre- and postsynaptic α2 receptors in the dorsal horn. Activation of these receptors depresses presynaptive C-fiber transmitter release and hyperpolarizes the postsynaptic membrane through the Gi-coupled potassium channel.[125,126] A different physiologic effect transpires, depending on the particular α subunit involved. The neuronal responses can be either inhibitory or excitatory.[127]

• BOX 72.6 Intrathecal Adrenergic Medications

FDA approved:	None	Maximum 24 h dose	Maximum concentration
Common use:	Clonidine		
		600 mcg	1000 mcg/mL

For example, the 2b subtype produces hemodynamic responses (primarily hypotension) while the 2a receptor is responsible for analgesia.[127,128] The mechanism of action of neuraxial α_2 agonists is similar to opioids in that they can exert effects on presynaptic and postsynaptic neurons.[128] On the presynaptic neuron, they bind to α_2 receptors of primary afferent neurons, resulting in hyperpolarization and depressed release of neurotransmitters involved in pain transmission. On postsynaptic neurons, α_2 agonists hyperpolarize the cell by increasing the transmission of potassium through G_i-coupled potassium channels.[126] Among the α-adrenergic agonists used for analgesia, clonidine remains the prototypical nonselective α_2 agonist, partly because it has been the most studied. Clonidine is a nonselective agonist that produces antinociception via interaction with the α 2a receptor. However, it also produces substantial hemodynamic side effects because of its interaction with the 2b receptor. The newer agent, dexmedetomidine, is a selective α_{2a} receptor agonist with analgesic and sedative properties, with less respiratory depression and fewer cardiovascular effects.[129–132] Dexmedetomidine demonstrates increased selectivity of the α 2a subunit than previous α-adrenergic agonists.[130,133] α-Adrenergic agonists have also been shown to activate spinal cholinergic neurons, which may contribute to their analgesic effects. In addition to their antinociceptive properties, α_2 agonists can produce dose-dependent sedation, presumably by inhibitory mechanisms involving the brainstem.[134,135]

α_2 Agonists have been administered intrathecally in humans since 1985. The antihypertensive medication clonidine is the most studied α_2 agonist for neuraxial use. Although it is FDA approved for epidural use only in cancer pain, clinical reports have shown it to be effective intrathecally and epidurally for non-malignant pain as well.[136,137] Intrathecal clonidine has been reported to provide significant analgesia in combination with opioids for neuropathic pain and cancer pain and has been used in the pediatric population for these reasons.[137] Clonidine has not consistently been shown to be effective as a single agent, but studies have shown it to prolong and enhance the effects of spinal and epidural anesthesia when co-administered with local anesthetics.[138–140] When added to opioids, clonidine can extend the duration of pain relief for labor analgesia and postoperative pain.[141–143] However, for acute pain, the evidence that adding clonidine to an epidural or intrathecal opioid is more effective than either analgesic alone is weak and inconsistent. Neuraxial clonidine has shown efficacy in treating central pain and spasticity after spinal cord injury.[144] Studies show that dexmedetomidine prolongs local anesthetic motor and sensory blockade compared to opioids.[143,144] α_2 Receptor agonists may also be suitable for patients suffering from neuropathic pain. In a randomized placebo controlled trial evaluating epidural clonidine in refractory reflex sympathetic dystrophy, Rauck et al. found that 300 μg of clonidine was equally effective but associated with fewer side effects than 700 μg.[145]

The interest in dexmedetomidine has grown in recent years because of its decreased cardiovascular and respiratory effects. Kanazi et al. showed, in a prospective, double-blind study, that 60 patients undergoing transurethral resection of prostate or bladder tumor under spinal anesthesia experienced a prolonged duration of motor and sensory blockade, with no increase in adverse hemodynamic effects or level of sedation.[140] Patients were randomized to three groups receiving either dexmedetomidine (3 μg) or clonidine (30 μg) added to bupivacaine or bupivacaine alone. These results suggest that low dose dexmedetomidine has similar analgesic efficacy to clonidine.

Clonidine has been studied extensively in animals and has produced no evidence of neurotoxicity.[146] The number of studies involving human exposure continues to grow and have not revealed any clinical evidence of neurotoxicity. Therefore clonidine appears to be a drug that can be administered safely in humans via the spinal route.

Conclusion

Since the 1980s, intrathecal drug delivery of opioids and nonopioid analgesics has become a promising option when more conservative therapies have failed. There are two main choices with regard to implanted intrathecal pump systems for the management of spasticity and cancer and chronic non-cancer pain. The challenges involved in the successful use of intrathecal therapy start with patient selection. Understanding the issues in selecting an appropriate candidate with cancer pain, chronic non-cancer pain, or spasticity will go a long way toward ensuring adequate therapy once the system is implanted. The main risks associated with the implantation of an intrathecal system are infection and catheter migration. Careful attention to good sterile technique during the surgical implantation and catheter anchoring can minimize these risks.

Key Points

- Intrathecal analgesia therapy has proven extremely beneficial to many patients; it is also associated with high costs, high maintenance, and risks requiring careful patient selection.
- The cost and invasive nature of an IDDS necessitate a careful evaluation to determine whether each individual patient is appropriate and likely to achieve benefit.
- A 2002 multi-center randomized trial compared CMM alone versus CMM plus an IDDS. The researchers found that cancer patients receiving CMM plus an IDDS had reduced pain, fewer drug toxicities, and prolonged survival than controls.
- The psychologist should not be asked to give "clearance" but rather act as an additional source of information about whether IDDS therapy is appropriate, the patient has rational expectations, and the treatment is likely to succeed or fail for an individual patient.
- There are only three FDA approved medications for use in IDDSs: morphine, baclofen, and ziconotide
- The use of intrathecal baclofen is typically reserved for conditions resulting in spasticity
- The high cost, high incidence of side effects, and narrow therapeutic window limit the use of ziconotide
- Granulomas are aseptic inflammatory masses composed of macrophages, neutrophils, and monocytes with granulation tissue. The formation of a granuloma at the catheter tip may cause loss of analgesic efficacy, progressive neurologic symptoms because of a mass effect on the spinal cord, and permanent neurologic injury.
- Iodinated contrast medium, and not gadolinium, should be injected through the side port to avoid encephalopathy or death from intrathecal gadolinium injection.

Suggested Readings

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Radiation Safety and Radiographic Contrast Agents

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Overview of Radiation Safety

Pain practitioners have come to rely on fluoroscopy and, to a lesser but growing extent, on computed tomography (CT) to facilitate image-guided pain treatment techniques. Fluoroscopy and CT employ ionizing radiation to produce the x-rays required for imaging. Understanding the physics and biology underlying the biologic effects of ionizing radiation will help *pain* practitioners minimize radiation exposure to their patients, other involved personnel, and themselves during image-guided injection. The basic elements of the fluoroscopy unit are shown in Figure 73.1. x-rays emanate from an x-ray tube, typically positioned beneath the table and the patient, to minimize radiation exposure. The x-rays pass through the table and the patient strikes the input phosphor of the image intensifier, where they are converted to visible light and detected by an output phosphor that transfers the signal to a digital camera for visual display on a monitor or transferred to film. The size and shape of the x-ray beam can be adjusted after exiting the x-ray tube and before entering the patient, from side to side by an adjustable linear collimator or in a circular, concentric fashion by an iris collimator. The C-arm allows variation in the axis of the x-ray beam in numerous planes relative to the patient.

In recent years, the use of CT has become more common, particularly among radiologists. With the advent of fluoroscopy units that can rotate around the patient and acquire images at numerous angles and then reconstruct the images in multiple planes, the distinction between CT fluoroscopy and traditional CT has become blurred. These CT fluoroscopy units yield data that can be reformatted in multiple planes and produce final images of the quality of conventional CT. However, acquiring images in multiple planes with either CT-fluoroscopy or conventional CT requires significantly greater radiation exposure than conventional fluoroscopy.[1] Usually, the superior anatomic information provided does not warrant the routine use of these advanced imaging modalities (see further discussion of radiation dose later in this chapter). Patients undergoing high-risk procedures where small variations in anatomy can alter the risk/benefit ratio of a given technique may benefit from CT fluoroscopy or conventional CT guidance.

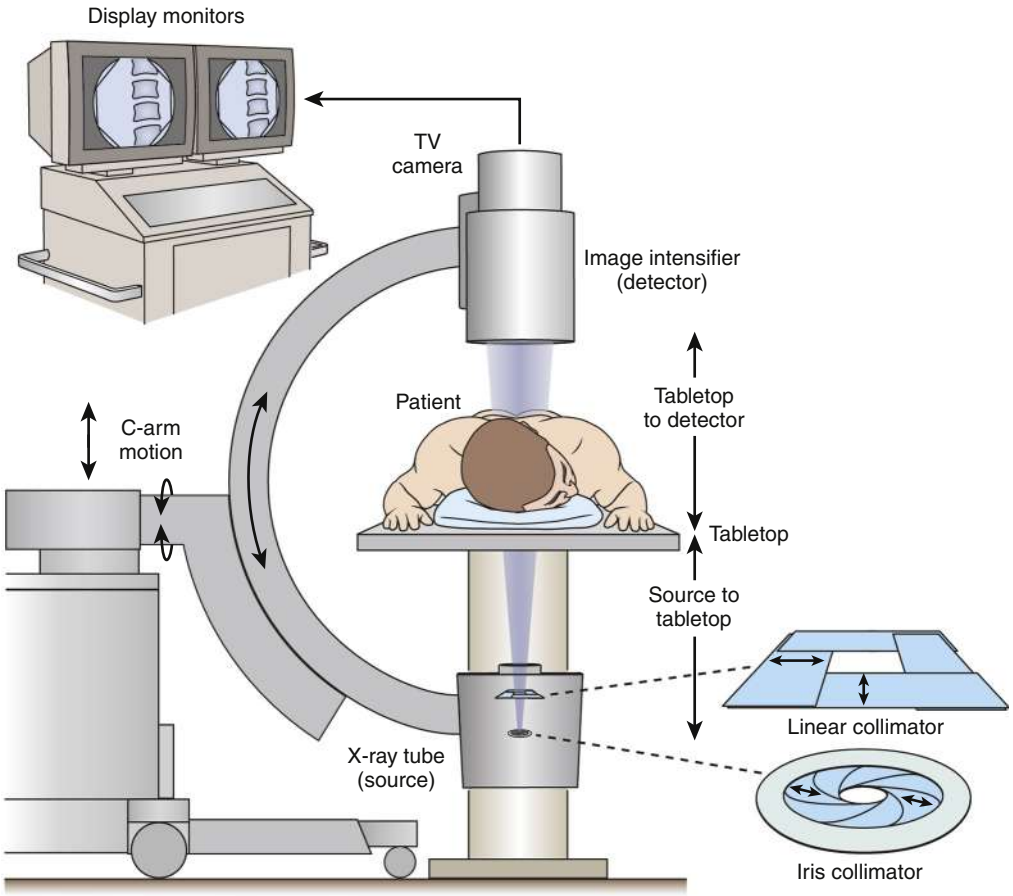
Basic Radiation Physics

Radiation is energy radiated or transmitted as rays, waves, or particles. x-rays are a portion of the electromagnetic radiation spectrum. As x-rays pass through matter, they impart sufficient energy to dislodge electrons (ionizing radiation), yielding free radicals that can lead to harmful biologic effects. In radiography, the x-rays that penetrate the body without effect emerge to strike an image intensifier where they are converted to visible light and can be displayed on a monitor or transferred to film, producing an image based on x-ray penetrability of various tissues.

Several factors and definitions are central to a basic understanding of radiation safety. The biologic effects of ionizing radiation are proportional to the time of exposure, whereas radiation exposure is inversely proportional to the *square* of the distance from the radiation source. Radiation exposure is expressed as roentgen or coulomb per kilogram, whereas the energy absorbed from radiation is expressed as the radiation absorbed dose (rad) or gray (Gy). Because different types of radiation can have different biologic effects, units of exposure are converted from rad to radiation equivalent in man (rem) or Sievert (Sv). The units used to express radiation exposure are listed in Table 73.1.[2] For x-rays, 1 roentgen (R) ~ 1 rad ~ 1 rem.

The electrical input to the tube that generates the x-rays can be varied to produce x-rays that differ in number and energy. Increased current applied to the x-ray tube (expressed as milliamps or mA) produces more x-rays, and the more X-rays that strike the image intensifier, the darker the image. Lengthening the exposure time also increases the number of x-rays reaching the image intensifier. Thus variations in current and exposure time are expressed as mAs (mA × s). An increased voltage (expressed as kilovoltage peak or kVp) applied to the x-ray tube results in x-ray emission at higher energy levels (i.e. with greater ability to penetrate). High kVp (75–125 kVp) and low mA (50–1,200 mA) were employed for fluoroscopy with short exposure times. This combination optimizes image quality while minimizing radiation exposure. High kVp/low mA combinations expose the patient to significantly less radiation than low kVp/high mA combinations. Modern fluoroscopy units typically employ automatic brightness control (ABC), which automatically adjusts kVp and mA to yield optimal brightness and contrast.

The x-rays generated during fluoroscopy are a form of ionizing radiation that can produce significant biologic effects. Small doses of ionizing radiation can produce molecular changes that take years to manifest in the form of cancerous transformation. Exposure to low doses of ionizing radiation is likely inconsequential because normal cellular mechanisms repair the damage. The International Committee on Radiation Safety Protection (ICRP) has produced estimates of the maximum permissible dose (MPD)



• **Figure 73.1** Diagram of the components of a typical fluoroscopy unit. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 2.1.)

TABLE 73.1 Units Used to Express Radiation Exposure and Dose

Term	Traditional Units	SI Units	Conversion
Exposure	Roentgen (R)	Coulomb/kg (C/kg)	1 R = 2.5×10^{-4} C/kg
Radiation absorbed dose	rad	Gray (Gy)	100 rad = 1 Gy
Radiation equivalent in man	rem	Sievert (Sv)	100 rem = 1 Sv

TABLE 73.2 Annual Maximum Permissible Radiation Doses

Area/Organ	Annual Maximum Permissible Dose
Thyroid	0.5 mSv (50 rem)
Extremities	0.5 mSv (50 rem)
Lens of the eye	0.15 mSv (15 rem)
Gonads	0.5 mSv (50 rem)
Whole body	0.05 mSv (5 rem)
Pregnant women	0.005 mSv to fetus (0.5 rem)

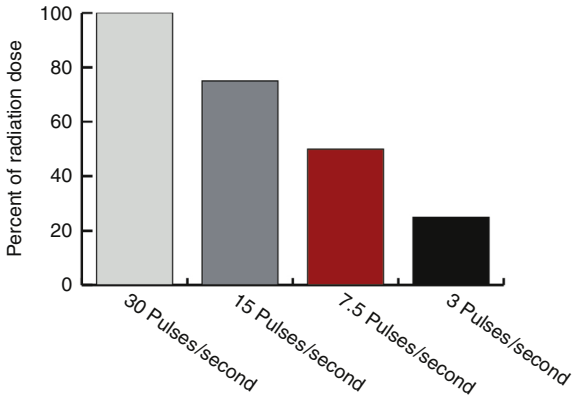
Data from the National Council on Radiation Protection and Measurements (NCRP). Report No. 116. Limitation of Exposure to Ionizing Radiation. Bethesda, MD: NCRP Publications; 1993.

of annual radiation to various organs (Table 73.2).[3] Exposure below these levels is unlikely to lead to any significant effects, but the ICRP recommends that workers should not receive over 10% of the MPD.

The use of fluoroscopy for interventional procedures grew rapidly during the late 1980s, leading to increased concerns about radiation exposure. In 1994, the United States Food and Drug Administration issued a public health advisory on serious radiation-related skin injuries resulting from fluoroscopic procedures. Today's equipment and techniques have dramatically reduced the risk of radiation exposure. Radiation exposure during a typical epidural steroid injection carried out with fluoroscopy and assuming the practitioner is at least 1 meter from the x-ray tube has been reported to be as low as 0.03 mR. In contrast, the typical entrance skin exposure during fluoroscopy ranges from 1 to 10 R per min. A typical single chest radiograph leads to a skin entrance exposure of 15 mR. Thus 1 min of continuous fluoroscopy at 2 R per min is equivalent to the exposure during 130 chest radiographs. The minimum target organ radiation doses that lead to pathologic effects are shown in Table 73.3. Radiation dermatitis still occurs in fluoroscopists with unknown long-term consequences.

TABLE 73.3 Minimum Target Organ Radiation Doses to Produce Organ Pathologic Effects

Organ	Dose (rad)	Dose (Gy)	Results
Eye lens	200	2	Cataract formation
Skin	500	5	Erythema
	700	7	Permanent alopecia
Whole body	200–700	2–7	Hematopoietic failure (4–6 week)
	700–5,000	7–50	Gastrointestinal failure (3–4 days)
	5,000–10,000	50–100	Cerebral edema (1–2 days)



• **Figure 73.2** Optimal spacing between the x-ray source and the patient to minimize radiation exposure. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 2.3.)

Minimizing Patient Radiation Exposure

Minimize Dose and Time

Practitioners using ionizing radiation should adhere to the ALARA principle ("As Low As Reasonably Achievable"), combining optimal techniques and shielding to minimize patient and personnel exposure.[4] Because no dose of ionizing radiation is without biologic effects and can be considered absolutely safe, radiographs should be used only when necessary, and the dose and exposure time should be limited. The dose is a factor of both the number of x-rays (proportional to mA × s of exposure) and the energy of the x-rays (proportional to kVp).[5] Modern fluoroscopy employs ABC, which automatically controls mA and kVp settings to optimize brightness and contrast while minimizing dose. However, if one chooses to use fluoroscopy in the manual mode (e.g. to increase penetration in an obese patient), kVp should be increased while minimizing mA. For an equivalent increase in exposure, the mA must be doubled, whereas kVp must be increased by only 15%. When using the ABC mode, the only element under practitioner control is the exposure time, and this should be held to the minimum required to complete the procedure. Short pulses of exposure, rather than continuous exposure, should be employed whenever feasible. Continuous fluoroscopy in the form of movies (cineradiography) and digital subtraction exposes patients to markedly higher doses than brief spot images. Many modern units include an option termed *the pulsed* mode for use instead of a continuous technique. This mode substitutes brief, periodic spot images separated by an interval without exposure (e.g. a new image is displayed one to two times per second). Use of this mode in place of continuous fluoroscopy can reduce overall exposure dramatically and is suitable for procedures in the pain clinic where continuous fluoroscopy is needed (e.g. while threading an epidural catheter or spinal cord stimulation lead; see Fig. 73.2).

Optimize the Position of the X-ray Tube

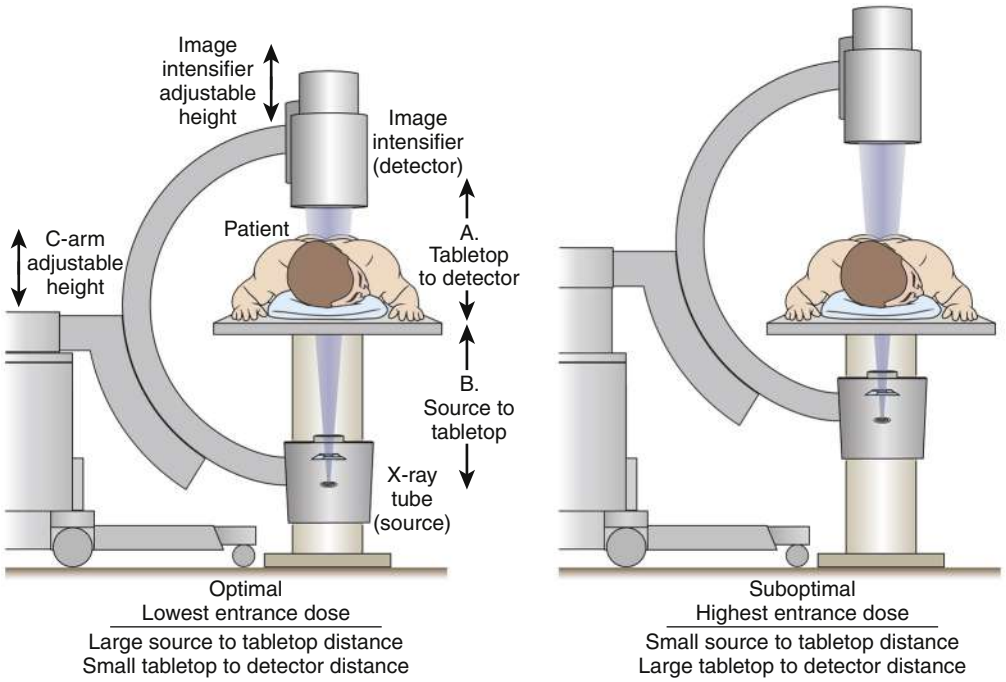
Radiation exposure to the patient is best minimized by ensuring an optimal distance between the patient and the x-ray tube (Fig. 73.3). When the x-ray tube is positioned close to the patient, a small area of skin will be exposed to radiation, but because of the close proximity of the x-rays, the dose to which this smaller area will be exposed is much higher. When the tube is positioned further from the patient, a larger area is exposed to a smaller dose of radiation. The x-ray tube should be positioned as far from the patient as possible without including unnecessary structures in the field of view.

Employ Shielding Whenever Possible

Using lead shielding can prevent exposure of regions adjacent to the area to be imaged from exposure to ionizing radiation. Small lead shields can be placed on the table underneath the patient, directly in front of the x-ray beam *before* it penetrates the patient to protect the gonads or the fetus, in rare instances where fluoroscopy is necessary for a pregnant patient. Although lead shields should be readily available in the fluoroscopy suite, they are seldom practical for use during image-guided injection of the lumbosacral spine because the shield lies directly in the path of the structures to be imaged.

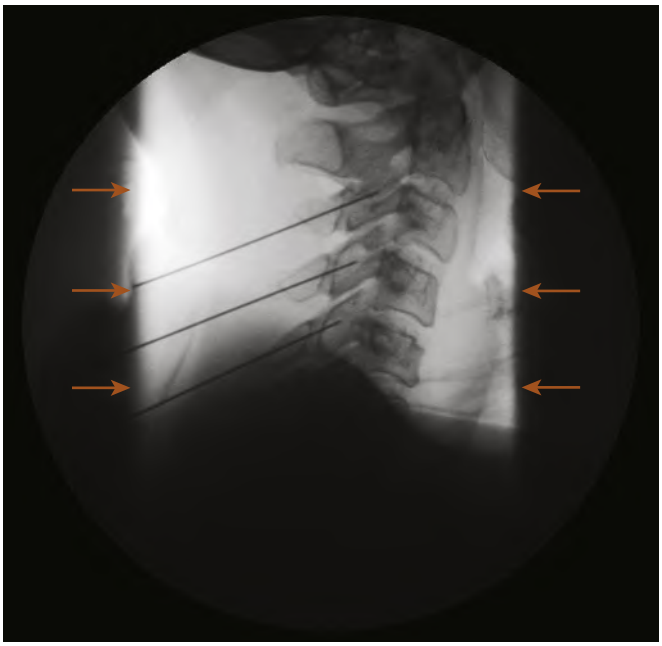
Employ Collimation

Fluoroscopy units have built-in mechanisms that allow the emitted x-ray beam to be reduced in size and changed in shape (or *collimated*), so the area of the patient exposed is minimized. All units had both linear and circular collimations. Linear collimation employs shutters that can be moved from either side of the exposure field and are helpful in imaging long, thin structures such as the spine (Fig. 73.4). Circular or "iris" collimation can be helpful when a small, circular area is to be imaged (Fig. 73.5). Collimation is also helpful in optimizing image quality because the ABC mode attempts to optimize the image quality by considering the exposure needed across the entire field of exposure, and it is often challenging to visualize radiodense and radiolucent areas in the same image. Useful employment of collimation can exclude areas of greatly varying radio-density to improve image quality by reducing the range of densities in the field. Two good examples are imaging of the thoracic spine, where the large density differences between the spine and the adjacent air-filled lungs can make it difficult to see the bony elements of the spine with any resolution. Linear collimation, which limits the field to the spine itself, dramatically improves image quality. Likewise, imaging of the cervical spine is fraught with the same difficulties when the air on

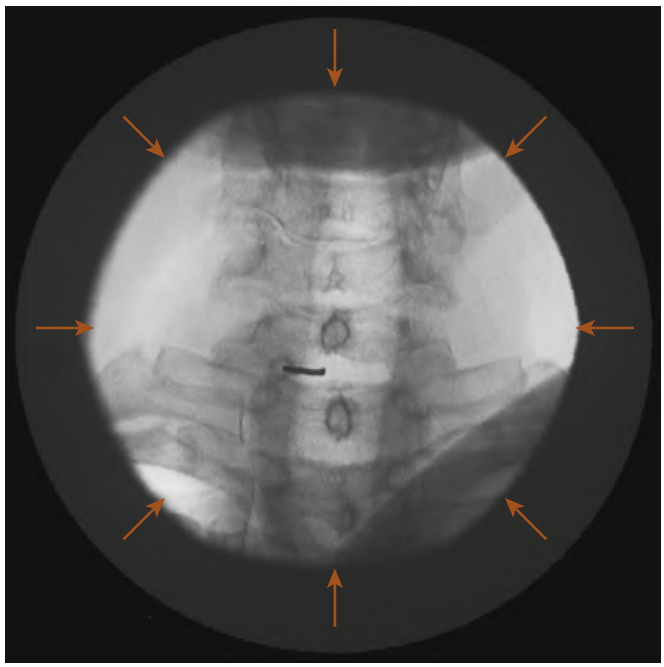


• **Figure 73.3** Effect of pulsed fluoroscopy on radiation dose (patient entrance skin dose). For example, by switching from continuous fluoroscopy (typically 30 pulses/second) to 15 pulses per second, dose savings of nearly 22% are achieved. (Adapted with permission from Mahesh M. AAPM/RSNA physics tutorial for residents Fluoroscopy: patient radiation exposure issues. *RadioGraphics.* 2001;21:1033-1045.)

either side of the neck is included in the x-ray field (see Fig. 73.4). Both linear collimation and circular collimation (see Fig. 73.5) can be used to limit the field to the area of interest, improve image quality, and reduce radiation exposure. Modern fluoro units may also allow *magnification* of the image by electronically magnifying the area of interest. Magnification allows better visualization of a smaller area but leads to increased radiation exposure as the system increases output to compensate for losses in gain. To minimize the



• **Figure 73.4** Use of adjustable (linear) collimator to decrease radiation exposure to the patient while improving image resolution by decreasing the range of tissue density in the image field. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 2.4.)



• **Figure 73.5** The use of an adjustable (iris) collimator to limit the field to the area of interest reduces radiation exposure to the patient and improves image resolution by decreasing the range of tissue density in the image field. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 2.5.)

dose to the patient, the largest field of view should be employed in conjunction with tightest collimation.

Minimizing Practitioner Exposure

Employ Proper Shielding

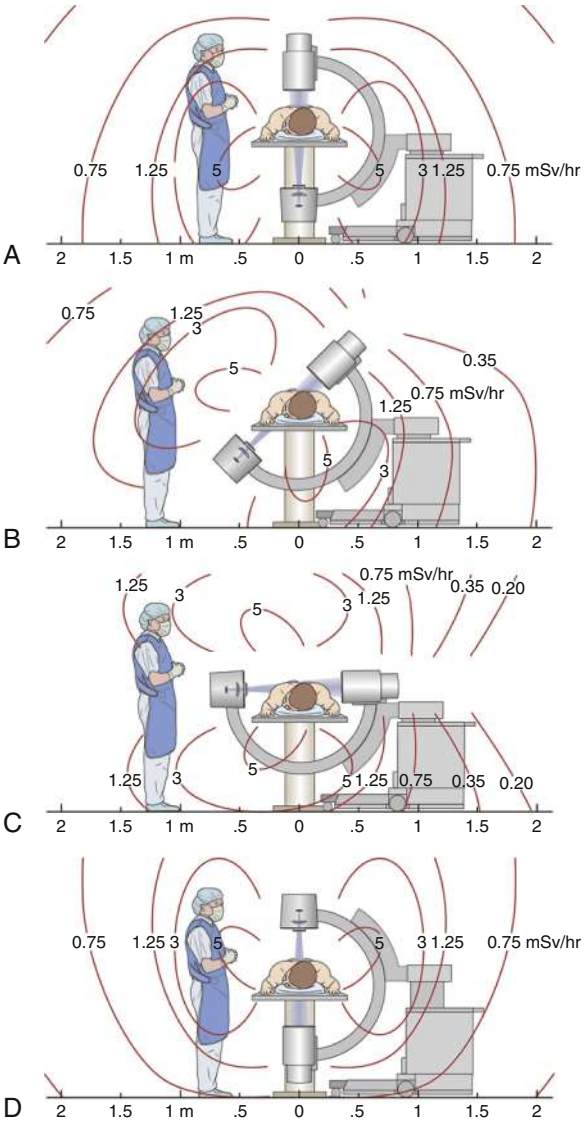
Only the personnel needed to conduct the procedure should be in the fluoroscopy suite. All personnel should be shielded with lead aprons *before* the use of fluoroscopy. The practitioner using the fluoroscopy unit should alert everyone in the room they are about to begin and ensure that personnel are shielded. Routine use of thyroid shields can minimize the long-term risk of thyroid cancer. Although protective lead gloves can reduce the exposure of the hands to radiation, they can produce a false sense of security. When leaded gloves are employed and the practitioner's hands are in the field of exposure, units with ABC will increase their output to compensate for the radiodense leaded gloves and negate their protective effects. Techniques that eliminate the practitioner's hands from direct exposure within the x-ray field should be used. Protective eyeglasses are available that dramatically reduce eye exposure during fluoroscopy; leaded eyewear is recommended for practitioners who accumulate monthly readings on collar badges above 400 mrem (4 Sv). Exposure levels in this range are typically encountered only in areas where continuous cine-angiography is frequently conducted (e.g. the cardiac catheterization laboratory).

Practitioner Position

The practitioner must understand the geometry of the radiation path as it passes from the x-ray tube to the image intensifier and adopt positions that minimize their exposure during fluoroscopy (Fig. 73.6). The dose drops proportionally to the square of the distance from the x-ray source. Thus standing as far from the x-ray tube as practical is the first means of minimizing exposure. Using an intravenous extension tube and taking a step back from the table during periods where contrast is injected under continuous or live fluoroscopy will reduce exposure. When the x-ray tube is rotated to obtain a lateral image, the practitioner should step completely away from the table beneath the x-ray tube and out of the path of the x-ray beam or move to the side of the table of the image intensifier. Inverting the C-arm so that the x-ray tube is above the table and the image intensifier is below the table is a means used by some practitioners to increase the C-arm's range of lateral movement beyond the typical 45° to 55° allowed by the unit. This practice dramatically increases the exposure to both patients and practitioners by bringing them near the x-ray source.

Optimizing Image Quality

Modern fluoroscopy units use ABC, which automatically adjusts mA and kVp to optimize image brightness and contrast while minimizing radiation exposure. These controls can be adjusted separately. An increased kVp produces x-rays of higher energy that penetrate without attenuation. Thus the resulting image is brighter with less contrast between different tissues, thereby reducing the image detail. The clarity of small structures, or image detail, can be improved by lowering kVP, reducing the distance between the patient and the image intensifier, and by using collimation to limit the field of exposure to only those structures of interest. Fluoroscopic images also have less sharpness at the periphery of the image because of a falloff in brightness and spatial resolution, a phenomenon called *vignetting*. Placing the structure of interest in the center of the image yields the maximum image detail. Finally, *pincushion distortion* occurs toward the periphery of the image because the x-rays emanate from a spherical surface and are detected on a flat surface.



• **Figure 73.6** Radiation exposure dosage during fluoroscopy. **A,** During routine use in the anterior-posterior plane, the x-ray tube (source) should be positioned below the patient and the detector above the patient to minimize radiation exposure to both the patient and the practitioner. **B,** The oblique projection results in markedly increased exposure to the practitioner. **C,** During use in the lateral projection, the practitioner should step behind the x-ray tube (source) to minimize radiation exposure. When it is necessary to work close to the patient during lateral fluoroscopy, the practitioner should step away from the x-ray tube and move to the side of the table opposite the x-ray tube to minimize exposure. **D,** Radiation exposure to both patient and practitioner is dramatically increased when the x-ray tube (source) is inverted above the patient. Some practitioners invert the C-arm to allow for a more extreme lateral angle (e.g. rotation beyond 35–45 degrees oblique to the side opposite the C-arm is impossible without inverting the C-arm on some units). Radiation exposure can be reduced by rotating the patient on the table and keeping the x-ray source below the table. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 2.6.)

TABLE 73.4 Radiation from Interventional Pain Procedures

Study	Procedures	Radiation Time	Radiation Readings
Botwin et al. 2002[11]	TF ESIs	5–38 s	0.7 mrem at the ring, 0.4 mrem at glasses, 0.3 mrem on the outside lead apron
Manchikanti et al. 2002[12]	ESI, facet, joint, intercostal, percutaneous adhesiolysis, spinal endoscopy, stellate ganglion, sympathetic	13.2 +/– 0.3 s/patient, 7.7 +/– 0.2 s/procedure	1.345 mrem/patient, 0.78 mrem/procedure
Zhou et al. 2005[13]	ESI, facet block, sympathetic blocks SI joint, lumbar discography	46.6 + /– 4.2, 81.5 +/– 12.8, 64.4 +/– 11, 50.6 +/– 41.9, and 146.8 +/– 25.1 s, respectively	
Kim et al. 2010[14]	Cervical NRBs, IL, TF ESIs epidurogram, facet, MBBs, psoas compartment, sympathetic	Average 80 s/procedure	1.345 mrem/patient, 0.78 mrem/procedure

ESI, Epidural steroid injection; *IL*, interlaminar; *MBBs*, medial branch blocks; *NRBS*, nerve root blocks; *SI*, sacroiliac; *TF*, transforaminal.
Radiation exposure well within safety limits (5 rem/year).

This results in an effect similar to that of a fisheye camera lens with a splaying outward of objects toward the periphery of the image. This can lead to particular difficulties when attempting to advance a needle using a coaxial technique if the needle is toward the periphery of the image. In the past several years, several manufacturers have developed electronic flat-plate detectors to replace conventional image intensifiers. Flat plate detectors employ a grid-like electronic detector that eliminates both vignetting and pincushion distortion, providing optimum image quality from the center to the peripheral portions of each image. Flat plate digital detectors are rapidly replacing traditional image intensifiers. Digital flat plate detectors can dramatically reduce radiation while improving image quality and eliminating the distortion of the image at the periphery of the detector that occurs with traditional image intensifiers.

Radiation From Interventional Pain Procedures

The most significant source of radiation exposure during interventional pain procedures is scattered radiation. Several factors determine this amount of radiation, including the experience of the radiographer and interventionalist, difficulty and length of the procedure, and the patient's habitus. The body weight of the patient and spinal pathology (e.g. spinal stenosis) have been correlated with radiation dose during interventional pain procedures.[6] The use of protective measures (lead apron, thyroid shield) reduces radiation exposure, as evidenced by lower scatter radiation readings.[7] Radiation-reducing gloves also reduce scatter radiation (reading at a location 20 cm from the table). Its attenuating effect is around 26%.[8] However, the use of lead gloves may make manipulation of the needle difficult. It also increases radiation because the ABC system automatically increases the kVp and current to compensate for the fuzzy image created by the gloves. Pulsed fluoroscopy reduces radiation compared to continuous fluoroscopy.[9] The incidence of inadequate image fluoroscopy with lumbar transforaminal ESI using pulsed fluoroscopy is 6%, and conversion to continuous fluoroscopy is sometimes required.[9] Despite the decreased quality of the image, it should be attempted first.

After interventional pain procedures, radiation readings are usually higher in badges worn outside the lead apron than inside the apron.[7] The highest scatter readings are at the knees during conventional fluoroscopy (x-ray tube below the table) and at the level of the physician's abdomen during lateral fluoroscopy.[10]

It appears that the amount of radiation from interventional pain procedures is within the MPD. Four studies on different interventional procedures showed safe readings in the eye, thyroid, gonads, extremities, or whole body (Table 73.4).[11–14] Two of the three studies showed zero readings in the badge inside the lead apron[11,12] while the other study calculated an annual radiation dose of 1.08 mSv under the apron.[14] Interestingly, the radiation doses were noted to be higher in a university setting than in private clinics, although in this study (the results in private practice groups were based on previously published studies).[13]

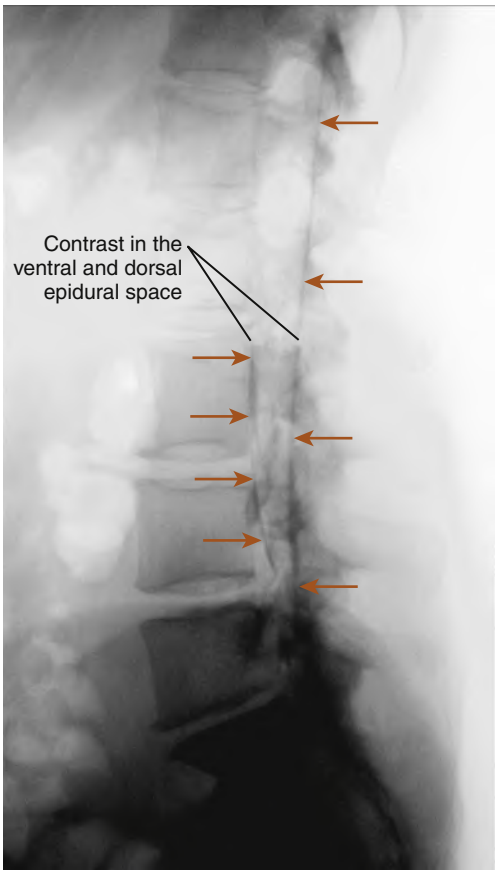
Although radiation exposure from interventional procedures appears to be within the safe limits, previously noted measures should be adopted. Reports of low radiation exposure may have instilled a false sense of security among pain physicians. A study showed that the usage of pulsed fluoroscopy is only around 10%.[13] Pain physicians in Korea wear lead aprons, thyroid shields, and lead glasses 93%–100%, 81%–100%, and 38%–40%, respectively.[15] The effectiveness of these measures and constant real-time coaching on optimal position[10] should be reinforced.

Overview of Radiographic Contrast Medium

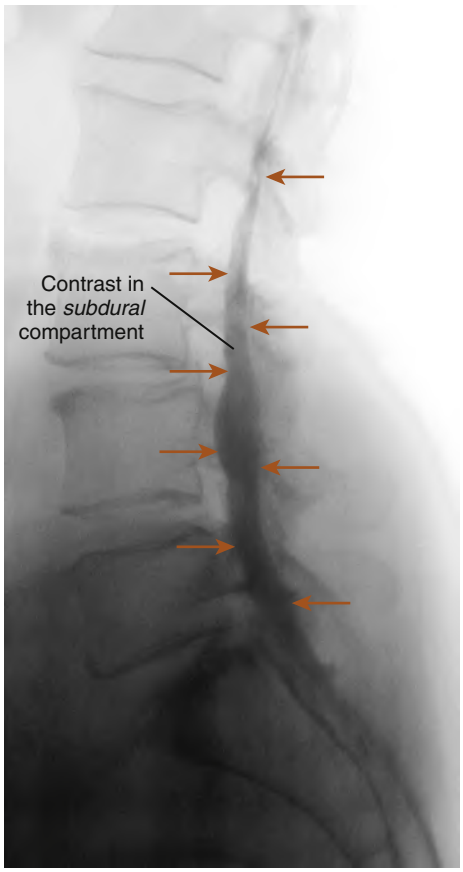
Iodine is the only element that has proven satisfactory as an intravascular radiographic contrast medium (RCM).[16] Iodine produces radiopacity, while the other portions of the molecule act as carriers for iodine, improving solubility and reducing the toxicity of the final compound. Organic carriers of iodine are likely to remain in widespread use in the foreseeable future. During image-guided injection, injection of RCM can prove invaluable in determining the final location and distribution of the injectate (Figs. 73.7–73.9). The use of RCM can improve the safety of many techniques by allowing for detection of intravascular (Figs. 73.10 and 73.11), subdural (see Fig. 73.8), or intrathecal (see Fig. 73.9) needle location before local anesthetic or steroid are placed.

Pharmacology of RCM

There are four chemical varieties of iodinated RCM that are widely used: ionic monomers, non-ionic monomers, ionic dimers, and non-ionic dimers.[17] On intravascular injection, all



• **Figure 73.7** Epidural contrast injection. This typical lateral lumbar epidurogram demonstrates the "double-line" or "railroad track" appearance of radiographic contrast in the anterior and posterior epidural space (*arrows*). (Reproduced with permission from Rathmell JP, Torian D, Song T. Lumbar epidurography. *Reg Anesth Pain Med.* 2000;25:541.)

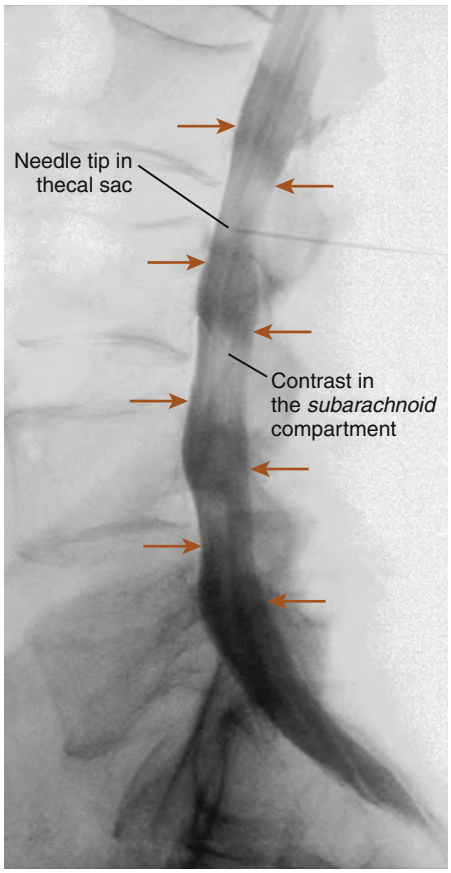


• **Figure 73.8** Subdural contrast injection. Injection of contrast in the subdural (epiarachnoid) space is recognized by the regular posterior border and irregular anterior border of loculated contrast collection on this lateral radiograph of the lumbar spine. The contrast is contained posteriorly by the dural membrane but extends only partially anteriorly, as it is contained by the thin arachnoid membrane. Compare with Figure 72.9, subarachnoid administration, where the contrast extends from the posterior to the anterior limits of the thecal space. Although the contrast does not extend to the anterior portion of the thecal sac, it is not limited to the epidural space. (Reproduced with permission from Ajar A, Rathmell JP, Mukerji S. Subdural compartment. *Reg Anesth Pain Med.* 2002;27:73.)

four are redistributed rapidly via capillary permeability to the extravascular space. They do not enter the interior of the blood or tissue cells. They are rapidly excreted, and more than 90% are eliminated via glomerular filtration within 12 h of administration. None of the four varieties exhibited marked pharmacologic actions. All RCM agents have a range of concentrations that vary in their radiopacity and viscosity. Because iodine is the element responsible for radiopacity, the iodine concentration in milligrams per milliliter represents the radiopacity. Non-ionic monomers are now used almost exclusively in pain medicine; non-ionic dimers offer increased radiopacity at low osmolar concentrations but are not in widespread clinical use and offer questionable clinical advantages.

Several important chemical properties determine the characteristics of RCMs for clinical use. Osmolality depends on the number of solute particles in the solution and is the highest for ionic contrast agents. Adverse reactions, particularly discomfort because of injection, have been reduced dramatically with the advent of low osmolar RCM. Contrast media with an osmolality below 500 mosm/kg of water are virtually painless. Radiopacity depends on the iodine concentration of the solution and therefore on the number of iodine atoms per molecule and the concentration of the iodine-carrying molecule in the solution. Digital subtraction electronically enhances the image, reducing the amount of contrast medium needed by a factor of two to three times. With the use of digital subtraction, RCM with as little as 150–200 mg/mL of iodine can be used even for intra-arterial use. Ionic molecules dissociate into cations and anions in the solution. Non-ionicity, or a molecule that does not dissociate in solution, is essential for myelography or use along the neuraxis, where inadvertent placement within the cerebrospinal fluid (CSF) is possible during the injection. The chemical properties of common RCMs used in clinical practice are compared in Table 73.5.

The most frequently used ionic monomers are diatrizoate (Urografin®), iothalamate (Conray®), and metrizoate (Isopaque®). All ionic monomers are salts of meglumine or sodium as the cation, and a radiopaque tri-iodinated fully substituted benzene ring as the anion. Ionic monomers are used for intravenous pyelography and similar applications. However, they have been completely replaced by the low osmolar, non-ionic RCM for many applications, including intrathecal administration. The most common non-ionic monomers in clinical use include iodixanol (Visipaque®), iohexol (Omnipaque®), iopamidol (Isoview®), and ioversol (Optiray®), and iohexol and iopamidol are labeled for intrathecal use. Non-ionic monomers appeared in the 1970s and represent



• **Figure 73.9** Subarachnoid (intrathecal) contrast injection. This typical myelogram demonstrates contrast within the thecal sac (*arrows*) on this lateral radiograph of the lumbar spine. The spinal cord and spinal nerves are visible as hypodense regions within the contrast collection. (Reproduced with permission from Rathmell JP, Torian D, Song T. Lumbar epidurography. *Reg Anesth Pain Med.* 2000;25:543.)

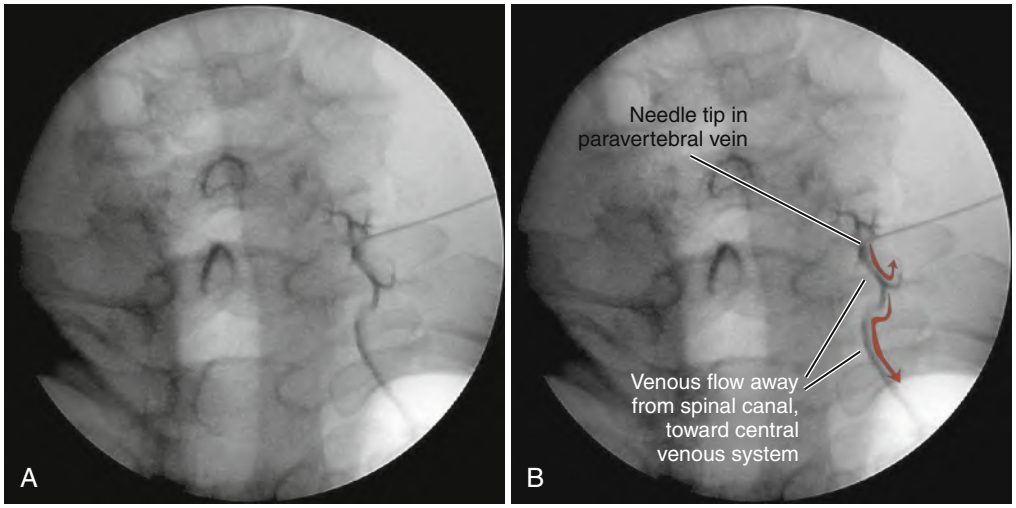
the most common RCM in clinical use. They are more stable in solution and less toxic than ionic monomers.

Adverse Reactions to RCM

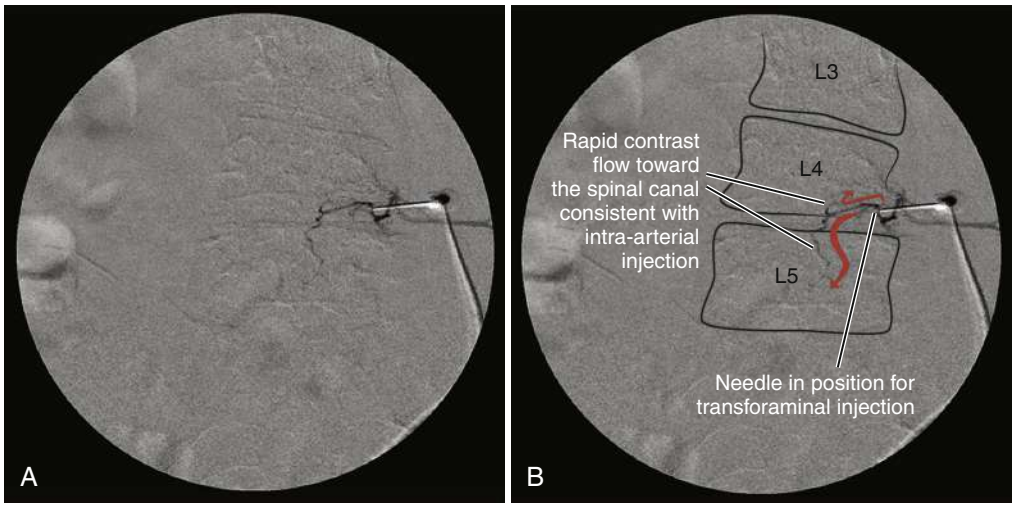
Modern contrast agents have been reduced, but are not eliminated, the risk of adverse reactions. To minimize the risk, RCM should be used at the smallest concentrations and in the smallest total dose that will allow adequate visualization. Adverse reactions associated with RCM can be divided into non-idiosyncratic or hypersensitive reactions (HRs). Nonidiosyncratic reactions are predictable, dose dependent, and related to the pharmacologic properties of the drug. HRs are dose-independent, not related to the pharmacologic properties of the drug, and unpredictable. HRs are further classified into allergic or non-allergic reactions. HRs were formerly called idiosyncratic reactions; they are also called anaphylactoid or non-allergic reactions, and the new (2020) and preferred term per the World Allergy Organization is "non-immunologic anaphylaxis." Allergy reactions require prior sensitization to culprit contrast medium (CM) with the production of immunoglobulin (Ig) E antibodies or allergen-specific T cells. Non-allergic HRs have similar manifestations as allergic reactions but are not immunoglobulin E (IgE) or T-cell mediated but are usually secondary to nonspecific mast cell release.[18] The risk of adverse reactions is significantly greater with the use of high-osmolarity ionic agents when compared with low osmolar, non-ionic agents. This discussion is limited to the risks associated with low osmolarity and non-ionic agents because they are used almost exclusively in pain medicine applications.

Nonidiosyncratic Reactions

Nonidiosyncratic reactions can be divided into chemotoxic reactions (chemical reactions to the iodine-carrying molecule) and osmotoxic reactions (those caused by the high osmolality of the CM). These nonidiosyncratic reactions are dose dependent; therefore this type



• **Figure 73.10** Intravenous contrast injection. **A**, Intravenous contrast injection is rarely seen on still images because the contrast material is rapidly diluted in the bloodstream. During real-time or live fluoroscopy, intravenous contrast injection appears as in this anterior-posterior radiograph of the cervical spine taken during the cervical transforaminal injection. The contrast can be seen flowing away from the spinal canal and toward the central venous circulation with the venous blood. **B**, Labeled image showing the direction of contrast flow. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 3.4.)



• **Figure 73.11** Intra-arterial contrast injection (digital subtraction). **A**, Intra-arterial contrast injection is rarely seen on still images because the contrast material is rapidly diluted in the bloodstream. During real-time or live fluoroscopy, intravenous contrast injection appears as in this anterior-posterior digital subtraction radiograph of the lumbar spine taken during the lumbar transforaminal injection. The contrast can be seen flowing toward the end organ (in this image, toward the lumbar spinal cord) with the arterial blood. The use of digital subtraction cine-radiography allows for the detection of intravascular injection with small doses of radiographic contrast material. **B**, Labeled image showing the direction of contrast flow. (Reproduced with permission from Rathmell JP. Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012: Fig. 3.5.)

TABLE 73.5 Comparison of Common Radiographic Contrast Agents Used in Clinical Practice[a]

Chemical Composition	Trade Name	Iodine (mg/mL)	Osmolality (mosm/kg H_2O)	Viscosity (cps @ 37 °C)	RCM Agent Type
Sodium/meglumine diatrizoate 30%	Urografin 150	146	710	1.4	Ionic, high-osmolar
Sodium/meglumine diatrizoate 67%	Urografin 325	325	1,650	3.3	Ionic, high-osmolar
Iohexol 180 mg/mL	Omnipaque 180	180	360	2.0	Non-ionic, low osmolar
Iohexol 300 mg/mL	Omnipaque 300	300	640	6.1	Non-ionic, low osmolar
Iopamidol 41%	Isovue 200	200	413	2.0	Non-ionic, low osmolar
Iopamidol 61%	Isovue 300	300	616	4.	Non-ionic, low osmolar

[a]The ionic, high-osmolar agent diatrizoate and the non-ionic, low osmolar agents iohexol and iopamidol. Iohexol and iopamidol are commonly used in image-guided pain treatment. These agents provide a non-ionic, low osmolar RCM that balances a low risk of adverse reaction, demonstrated safety for intrathecal use, and sufficient radio-opacity to identify intravascular and intrathecal placement.

RCM, Radiographic contrast media.

of reaction should be exceedingly rare in patients receiving small volumes of RCM required to facilitate needle localization during image-guided pain treatment.

Chemotoxic reactions are rare and may result in direct organ toxicity, including cardiac (direct and prolonged decrease in cardiac contractility), neurologic (seizures), and renal toxicity (oliguria, impaired creatinine clearance, and reduced glomerular filtration rate that may progress to acute renal failure).[19]

Osmotoxic reactions are much more common in high-osmolar contrast media, where the osmolality of the RCM can reach several times that of physiologic osmolality of 300 mosm/kg H_2O[20]; toxic reactions have been dramatically reduced with the advent of low osmolar, non-ionic agents such as iohexol and should be exceedingly rare after administration of the small volumes used in pain medicine applications. Hyperosmolar reactions include erythrocyte damage (hemolysis), endothelial damage (capillary leak and edema), vasodilation (flushing, warmth, hypotension, cardiovascular collapse), hypervolemia, and direct cardiac depression (reduced cardiac contractility).

Hypersensitivity Reactions

HRs are mostly anaphylactoid in nature, comprising 80%–90% of HRs to iodinate contrast media (ICM). Acute HRs occur within 1 h, usually within 20 min of CM administration. Delayed HRs occurred 1 h to one week later. These are usually mild and cutaneous in nature.[21–23] The risk of anaphylactoid reaction is increased in patients with a previous reaction to RCM. Other factors include asthma, atopy, drug allergy, female sex, and severe cardiovascular disease.[24,25] For patients with seafood allergy, their risk of a reaction

to RCM appears to be similar to that of patients with other food allergies, or asthma, and experts concluded that allergy to shellfish does not increase the reaction to contrast more than other allergies.[26,27] Iodine cannot be an allergen since it is found throughout our body and added to most salt and medicinal compounds.[26] Patients who develop reactions to povidone-iodine skin prep react to allergens in the solution rather than iodine.

Recognition and Treatment of Reactions to RCM

The American College of Radiology (ACR) classified the reactions into mild, moderate, or severe; it can be life threatening (Table 73.6).[16] The incidence of these reactions following the use of small volumes of RCM in pain medicine is extremely rare. A recent study noted the absence of HRs after 6471 pain procedures; 108 patients had previous ICM allergy.[28] The absence of breakthrough reactions (reactions in patients with previous HRs) after an interventional pain procedure was previously reported in six patients injected with the same culprit ICM.[18] The authors ascribed the lack of breakthrough reactions to the small volumes injected, concomitant injection of steroids, and the extravascular route. In another study, 25 patients who had extravascular ICM injections (gastrointestinal, genitourinary, abdominal cavity, CSF) had no breakthrough reaction compared to 19% in patients who had intravascular ICM injection.[29]

The overall reaction rate to intravenous administration of large volumes of low osmolar ICM is 0.6%.[21,30,31] The overall incidence of HRs and severe HRs is 0.7% and 0.01%, respectively.[25] Most

TABLE 73.6 The Severity of HRs Acute HRs

Mild	
Mild signs and symptoms are self-limited without evidence of progression.	
Allergic-like	*Physiologic*
Limited urticaria/pruritus	Limited nausea/vomiting limited
Cutaneous Edema	Transient flushing/warmth/chills
Limited "itchy"/"scratchy" throat	Headache/dizziness/anxiety/altered taste
Nasal congestion	Mild hypertension
Sneezing/conjunctivitis/rhinorrhea	Vasovagal reaction that resolves spontaneously
Moderate	
Signs and symptoms are more pronounced and require medical management. Some of these reactions have the potential to become severe if not treated.	
Allergic-like	*Physiologic*
Diffuse urticaria/pruritus	Protracted nausea/vomiting
Diffuse erythema, stable vital signs	Hypertensive urgency
Facial edema without dyspnea	Isolated chest pain
Throat tightness or hoarseness without dyspnea	Vasovagal reaction that requires and is responsive to treatment
Wheezing/bronchospasm, mild/no hypoxia	
Severe	
Allergic-like	*Physiologic*
Diffuse edema, or facial edema with dyspnea	Vasovagal reaction resistant to treatment
Diffuse erythema with hypotension	Arrhythmia
Laryngeal edema with stridor and/or hypoxia	Convulsions, seizures
Wheezing/bronchospasm, significant hypoxia	Hypertensive emergency
Anaphylactic shock (hypotension + tachycardia)	

Adapted from the American College of Radiology manual (with permission).

TABLE 73.7 Suggested Treatment for Reactions to Radiographic Contrast Media of Moderate Severity

Adverse Reaction	Suggested Treatment
Urticaria	Diphenhydramine 25–50 mg PO, IM, or IV
Anxiety	Diazepam 5–10 mg PO or midazolam 1–2 mg IV
Bronchospasm	Mild: Inhaled albuterol
	Severe:
	Hydrocortisone 100 mg IV
	Epinephrine 0.05–0.1 mg SQ, IM, IV
Anaphylaxis	Epinephrine 0.01 mg/kg SQ, IM, IV (maximum adult dose 0.5 mg)

cases are mild (83%), and the incidences of moderate and severe HRs are 16% and 1%, respectively. Mild reactions in those receiving intravenous contrast include flushing anxiety, nausea, arm pain, pruritus, vomiting, headache, and mild urticaria. These are generally mild and self-limiting, and require no specific treatment. Occasionally, an oral antihistamine (diphenhydramine, 25 mg) can be useful in managing pruritus and anxiety. More serious reactions include more pronounced severity of mild symptoms and moderate degrees of hypotension and bronchospasm. The suggested treatments for moderate reactions are listed in Table 73.7.

Severe reactions are life-threatening, occurring in 0.01%–0.04% of those receiving intravenous RCM, and include convulsions, unconsciousness, laryngeal edema, severe bronchospasm, pulmonary edema, severe cardiac arrhythmias, and cardiovascular collapse.[16] Treatment of these life threatening reactions is urgent, necessitating the immediate availability of full resuscitation equipment and trained personnel, along with a routine practice for responding to these rare events. The airway must be secured, and oxygen, mechanical ventilation, external cardiac massage, and electrical cardiac defibrillation must be administered as required. Epinephrine is the drug of choice for the treatment of anaphylaxis; the usual adult starting dose is 0.01 mg/kg (maximum of 0.5 mg) subcutaneously, intravenously, or intramuscularly. Death may ensue following this type of severe adverse reaction; the incidence is not known with accuracy but likely lies between 1/14,000 and 1/170,000 intravenous administrations of RCM.

Prevention of Reactions to RCM

Any history of HRs should be recorded in the patient's chart: the CM used, amount injected, and the signs, symptoms, and treatment given. Prevention of breakthrough reactions involves identifying the culprit CM and identifying the factors that predispose patients to adverse reactions when they receive the RCM.

The risk of breakthrough reactions is increased in those who had severe initial HRs, diabetes, drug allergies, urticaria, and chronic steroid intake.[32] No known premedication regimen can reliably eliminate the risk of severe reactions to RCM.[24] The most common strategies suggested combining pre-treatment with corticosteroids (e.g. oral prednisone 50 mg doses 12 and 2 h before RCM administration) and antihistamines (e.g. oral diphenhydramine 50 mg doses 1–2 h before RCM administration). Some authors recommend the addition of H_2-antagonists (e.g. oral ranitidine). The protective effect of steroids has not been consistent.[24,33] Additionally, an increase of 40–150 mg/dL of blood sugar can occur within the first 24–48 h (ACR manual). Changing the ICM and premedication with antihistamine has been shown to reduce breakthrough HRs.[33,34] It has been our practice to avoid radiographic contrast altogether in those at elevated risk for an adverse reaction. Most procedures in pain medicine can be performed safely without the use of radiographic contrast. In some instances (e.g. epidural placement), the location can be established using the loss of resistance alone, and the final needle position can be verified using anteroposterior and lateral radiography without contrast. However, some injections should not be attempted without radiographic contrast injection (e.g. transforaminal injection), in which case, injection of contrast under live or real-time fluoroscopy (with or without digital subtraction) is the only means to detect intra-arterial needle location and to prevent catastrophic injection of particulate steroids directly into critical vessels supplying the spinal cord.

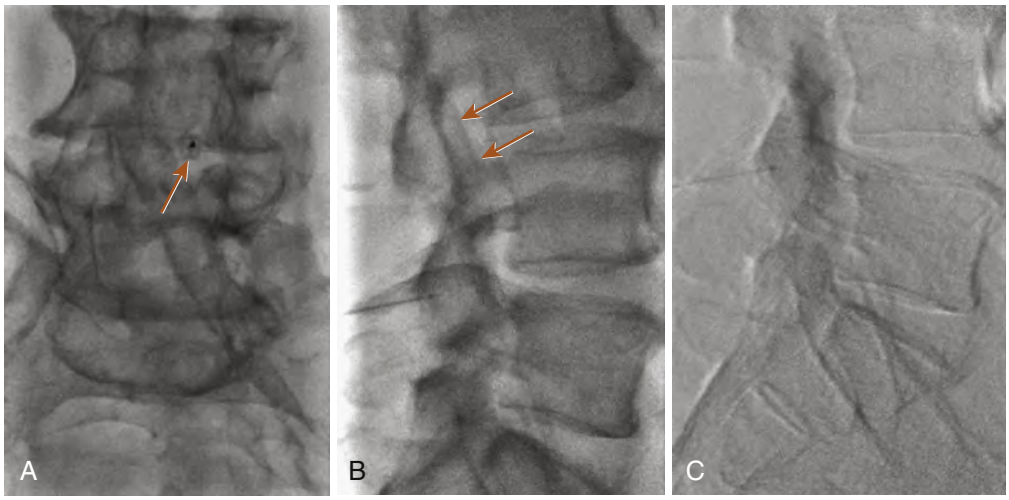
A multi-specialty multi-society group developed practice guidelines for RCM. The position statements (PS) and recommendations related to HRs are discussed in conjunction with gadolinium based contrast agents (GBCAs).[35]

Use of Gadolinium as an Alternative to Iodinated RCM

GBCAs, for example, gadopentetate dimeglumine (Magnevist), are commonly used intravenous contrast agents used to enhance vascular structures during diagnostic magnetic resonance imaging (MRI). Gadolinium chelates also have an intrinsic ability to attenuate x-rays and have been used successfully in place of ICM for angiography and spinal injections used in image-guided pain treatment. The radio-opacity of gadolinium is less than that of ICM (Fig. 73.12A, B).[36] Of the GBCAs, images with gadobutrol are more conspicuous because of their higher concentration (Table 73.8)[37] Nonetheless, 1–3 mL of undiluted gadopentetate dimeglumine (Magnevist) has been used successfully and reliably to identify the epidural space; the visualization can be further enhanced through the use of digital subtraction in combination with gadolinium (Fig. 73.12C).

GBCAs have been used as an alternative to iodinated contrast agents (ICM) in patients with known HRs to ICM.[36] This is because GBCAs have a lower incidence of HRs when compared to ICM: 0.013%–0.48% immediate HRs and 0.001%–0.01% severe reactions versus 3%–13% for immediate and 0.01%–0.04% for severe reactions for ICM.[21] Similar to the ICMs, HRs to GBCAs are mostly mild in nature. The risk factors are the same as those for ICM.[38,39] HRs are more common with GBCAs that are macrocyclic and ionic than the linear non-ionic GBCAs, partly because of their higher osmolality.[40,41] Among the linear ionic GBCAs, linear ionic GBCAs with high protein binding (gadofesveset, gadobenate, gadoxetate) have higher rates of immediate allergic-like reactions than ionic linear chelates without protein binding (gadopentetate).[42] Linear GBCAs that do not readily bind to proteins (gadodiamide) have lower rates of immediate allergic-like reactions than macrocyclic agents (gadobutrol, gadoteridol, gadoterate). Macrocyclic agents do not bind to proteins.

GBCAs are classified as either linear or macrocyclic based on the nature of the chelating agent.[43] For macrocyclic agents, Gd ions are caged at the center of the chelating agent, whereas linear GBCAs have an open-chain chemical structure in which the



• **Figure 73.12** Utility of digital subtraction fluoroscopy for visualization of the gadolinium-based contrast epidurogram. A nonselective epidural steroid injection was performed on a 62-year-old male at L4-L5 employing an interlaminar approach. **A,** Right anterior oblique (RAO) projection of the lumbar spine shows a needle (*arrow*) inserted into the interlaminar space at L4-L5. **B,** Conventional fluoroscopy permits visualization of an epidurogram in the lateral projection (*arrows*). **C,** Digital subtraction fluoroscopy in the lateral projection more clearly demonstrates the distribution of the gadolinium chelate in the epidural space. (Adapted with permission from Shetty SK, Nelson EN, Lawrimore TM, Palmer WE. Use of gadolinium chelate to confirm epidural needle placement in patients with iodinated contrast reaction. *Skeletal Radiol.* 2007;36:301-307, Fig. 2.)

TABLE 73.8 Gadolinium Based Contrast Agents

Gadolinium Based Contrast Agent	Type, Stability[b]	Concentration mmol/mL	Usual MRI Dose mmol/kg (mL dose in 70 kg person)[c]	Lowest Dose Associated With Gadolinium Deposition in the Brain (70 kg person)[d]
Gadodiamide (Omniscan®)	Nonionic linear, Low	0.5	0.1 (14 mL)	37.8 mL
Gadoversetamide (Optimark®)	Nonionic linear, Low	0.5	0.1 (14 mL)	37.8 mL
Gadobenate dimeglumine (MultiHance®)[a]	Ionic linear, Intermediate	0.5	0.1 (14 mL)	37.8 mL
Gadopentetate dimeglumine (Magnevist®)	Ionic linear, Intermediate	0.5	0.1 (14 mL)	37.8 mL
Gadofesveset trisodium (Ablavar®, Vasovist®)	Ionic linear, Intermediate	0.25	0.03 (8.4 mL)	75.6 mL
Gadoxetate disodium (Eovist®, Primovist®)[a]	Ionic linear, Intermediate	0.25	0.025 (7 mL)	75.6 mL
Gadoteridol (ProHance®)	Nonionic macrocyclic, High	0.5	0.1 (14 mL)	37.8 mL
Gadobutrol (Gadavist®)	Nonionic macrocyclic, High	1	0.1 (7 mL)	18.9 mL
Gadoterate meglumine (Dotarem®)	Ionic macrocyclic, High	0.5	0.1 (14 mL)	37.8 mL

[a]Used for liver magnetic resonance imaging.

[b]Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol.* 2016;34:3–9.

[c]Usual radiology doses for magnetic resonance imaging (MRI) of the brain or body parts.

[d]0.27 mmol/kg is the lowest dose noted with gadolinium deposition in the brain of patients with chronic renal failure.

Reprinted from Benzon HT, Liu BP, Patel AS, and Benzon HA. Caution of using gadolinium-based contrast agents in interventional pain procedures. *Anesth Analg.* 2018;127:1452–1456.

chelating agent is wrapped around the Gd ion.[44,45] Macrocyclic agents are more stable and dissociate less. Among linear GBCAs, non-ionic GBCAs are less thermodynamically stable than ionic GBCAs and therefore release more gadolinium than ionic agents (Table 73.8). The stability of the GBCA explains the more frequent occurrences of nephrogenic systemic fibrosis (NSF) and gadolinium brain deposition/retention with linear GBCAs than with macrocyclic agents. These adverse events are secondary to the release of gadolinium—a toxic ion. Gadolinium is released through the dechelation of the ligand.

A multi-specialty multi-society practice guideline on HRs to contrast media issued the following recommendations:[35]

- When an HR occurs, the interventional physician should document the incident. The report should include the name and volume of injected CM.
- The physician should be notified immediately if a patient scheduled for a procedure with contrast injection has a history of HR to CM.
- Patients with a history of mild HRs to CM may receive appropriate pretreatment and receive a different low osmolar non-ionic CM if the culprit ICM is known.
- Patients with a history of moderate or severe HRs to ICM should be pretreated and injected with a different low osmolar non-ionic ICM, if culprit ICM is known, and if alternative contrast choices such as GBCM or air (with CT) are contraindicated.
- In the absence of an immediate reaction, prophylaxis for late reactions is not recommended, and treatment should be symptomatic.
- Patients with a history of true IgE-mediated allergic HRs and a positive skin test (performed within six months of HR) should receive premedication with steroids and H1 antihistamine medication.
- Patients with a history of true IgE-mediated allergic HRs should be injected with a different ICM, which is skin test-negative.
- Acute HRs should be managed symptomatically.
- Recommendations for the duration of monitoring in patients with a history of HR and CM.
- Premedicated patients with a history of mild HRs and no symptoms following exposure to CM: 30 min
- Non-premedicated patients with a history of mild HRs and no symptoms following exposure to the same CM: 30 min
- Patients with a history of moderate/severe HRs but no reaction in the first 15 min (irrespective of premedication status): 30 min–1 h
- For staff associated with interventional pain procedures, there should be an annual review of (1) grading system for the severity of hypersensitivity reactions, (2) components of documentation for witnessed or historical HRs, (3) emergency preparedness of the staff, and (4) steps involved in cardiopulmonary resuscitation.
- Emergency equipment, including airway supplies, defibrillators, and cardiovascular support medications, should be immediately available during interventional procedures involving the administration of CM, especially in patients with a history of HR to CM.

The continued use of GBCAs has been questioned because of adverse events.[46] Besides NSF, including trending gadolinium brain/deposition/retention and catastrophic encephalopathy after unintentional intrathecal (IT) gadolinium injection.

Nephrogenic Systemic Fibrosis

NSF is characterized by cutaneous and systemic symptoms resulting from gadolinium administration, with renal insufficiency being the dominant risk factor. NSF is related to free gadolinium after the ion is released from its chelate (dechelation).[47] Gadolinium activates the production of profibrotic cytokines, resulting in fibroblast formation. Gadolinium is a lanthanide element, and lanthanides are known to cause fibrosis and enhance the polymerization of skin collagen *in vitro* and fibril formation. The symptoms include thickened skin and subcutaneous tissue resulting in stiffness and contractures.[48,49] There is also fibrosis of internal organs.[49] Thomsen et al. categorized the GBCAs according to the risk of development of NSF.[50] The GBCAs with the highest risk, because of the greatest dissociation, include the linear non-ionic GBCAs gadodiamide (Omniscan^{R}) and gadoversetamide (Optimark^{R}) and the linear ionic gadopentetate (Magnevist^{R}). The intermediate-risk group consists of the linear ionic agents gadobenate (MultiHance^{R}) and gadoxetate (Eovist^{R}, Primovist^{R}). The lowest risk group, that is, the GBCAs with the lowest degree of dissociation, includes the macrocyclic agents gadoteridol (ProHance^{R}), gadobutrol (Gadavist^{R}), and gadoterate (Dotarem^{R}).

There are several guidelines on the use of GBCAs in relation to NSF, all related to the use of GBCAs in radiologic diagnostic procedures involving intravascular administration.[16,43,50] The recommendations of the multi-specialty multi-society practice guideline on NSF to contrast media include:[35]

- Patients at risk of developing NSF should be identified before administering a GBCA.
- Screening for renal function in interventional pain procedures may not be necessary with stable macrocyclic GBCAs (gadobutrol, gadoteridol, gadoterate) and the linear ionic GBCA gadobenate dimeglumine.
- The lowest possible dose of GBCA to obtain necessary clinical information should be administered.
- In *interventional* pain procedures, the low-risk macrocyclic (gadoteridol, gadobutrol, gadoterate) and medium-risk linear/ionic (gadoxetate, gadobenate dimeglumine) GBCAs can be administered to patients with moderately reduced kidney function (CKD3, eGFR between 30 and 59 mL/min/1.73 m^2).
- In *interventional* pain procedures, when GBCA is necessary, low risk macrocyclic (gadoteridol, gadobutrol, gadoterate) and medium-risk linear/ionic (gadoxetate, gadobenate dimeglumine) GBCAs may be used with caution in patients with severely reduced kidney function (CKD4, eGFR 15–29 mL/min/1.73 m^2; CKD5, eGFR <15 mL/min/1.73 m^2) and those on dialysis.
- In *interventional* pain procedures, GBCAs in the high-risk category (gadodiamide, gadoversetamide, gadopentetate dimeglumine) are contraindicated in patients with CKD 4 or 5 (eGFR <30 mL/min/1.73 m^2), patients with end-stage renal disease on chronic hemodialysis, and patients with acute kidney injury.
- In anuric patients with no renal function, GBCA should be avoided. Instead, the lowest dose of iodinated contrast medium should be considered if contrast is essential.

Brain Deposition/Retention

After gadolinium is released from its ligand, transmetalation—the exchange of gadolinium for other endogenous ions such as iron, copper, zinc, or calcium—occurs in tissues prone to this process (e.g. dentate nucleus, globus pallidus, lentiform nucleus, and pulvinar of the thalamus). The gadolinium deposits appear as high-relaxivity complexes that cause visibly increased T1 signal intensities on non-contrast MRI examinations and remain for months to years after exposure.[51] The deposition of gadolinium in the brain is dose-related,[52,53] case reports showed patients who had

5–35 MRIs,[46] some for follow-up of their brain tumors. Gadolinium brain deposition/retention is not associated with kidney function.[54] Besides the brain, gadolinium has been demonstrated in the liver, skin, and bone.[55,56] Similar to NSF, the gadolinium deposition/retention in the brain occurs more with the linear GBCAs such as gadodiamide and gadopentetate and at much lower levels with the macrocyclic chelates. Current research suggests that it is almost certain that all GBCAs, regardless of structure or ionicity, are associated with some level of gadolinium deposition.[51]

No definite clinical consequences of GBCA retention in the brain have been established.[57,58] The symptoms reported by patients include flu-like symptoms, headache, bone/joint pain, vision/hearing change, skin changes, and digestive and chest symptoms.[59] These symptoms may not be attributed to gadolinium brain deposition since these occur within six weeks of exposure, hence overlapping with the symptoms of NSF. A large population-based study (246,557 patients; 99,739 received gadolinium) showed that the incidence of parkinsonism was the same in the patients who received at least one gadolinium dose (1.16%) than in patients who had non-contrast MRI (1.17%).[60] Knowledge in this area is incomplete, and studies are evolving. There has been no documented gadolinium deposition in the brain after an interventional procedure, partly because most patients referred to the pain clinic already had a contrast-enhanced MRI.

Published practice guidelines apply to diagnostic radiologic procedures involving large volumes of intravascular GBCA injection.[61] Recommendations from these guidelines relevant to interventional pain procedures include limiting the use of GBCA to only when medically necessary, dose not exceeding recommended dosages, avoidance of repeated GBCA administrations, and monitoring the literature for development.

The recommendations of the multi-specialty multi-society practice guideline on NSF to contrast media include:[35]

- Interventional pain physicians should be aware of patients who have incurred a gadolinium administration burden from multiple gadolinium-enhanced MRI examinations.
- Gadolinium is a drug that should be used with caution in interventional pain procedures. It should be administered only when necessary.
- Several factors need to be considered when selecting a GBCA, including diagnostic efficacy, rate of adverse reactions, dosing/concentration, radio-opacity, and propensity to deposit in organs such as the brain.
- Ongoing research and emerging evidence need to be monitored, and relevant information incorporated into clinical practice as this field of inquiry evolves.

Encephalopathy After Unintentional Intrathecal Gadolinium Injection

There have been case reports of encephalopathy after unintentional intrathecal (IT) injection of gadolinium after interventional pain procedures[62–65] and after diagnostic settings.[66–69] In pain medicine settings, the IT injection occurred during an attempted epidural injection[62,64] or a minimally invasive lumbar decompression procedure.[65] The volume injected ranged from 1.5 mL–5 mL. All the patients showed gadolinium in their subarachnoid space on MRI.[62,64,65] One patient had leg pain and spasms, one had to be intubated, and another patient died 14 days later. The patients in the non-pain settings received intrathecal injections of 10–20 mL. One patient took 56 days to recover,[66] while another showed no sequelae after 60 days (**Li**). The third patient had visual disturbances at one month,[67] while the fourth patient stayed in intensive care for at least two months.[69]

Radiologists inject gadolinium intrathecally when they evaluate dural leaks, hydrocephalus, and other CSF disorders (arachnoid cyst communications, aqueductal stenosis, obstruction of the fourth ventricle) and in their investigation of the glymphatic pathway.[70–72] Other authors prospectively looked at the safety of an intrathecal injection of 0.5 mL gadobutrol and 3 mL iodixanol (Visipaque^{R}) in 100 patients.[72] The adverse events included severe HA (28%) and severe nausea (34%) that resolved after four weeks. A patient with a known allergy to ICM developed anaphylaxis. The authors concluded that the intrathecal injection of 0.5 mL gadobutrol was safe.[72] The safety of these injections may be explained by the dilution of the gadolinium with either 4 mL saline or 1 mL CSF or 5 mL ICM (e.g. iohexol) and the slow duration of injection, e.g. over a 3 min period.[73] This is in contrast to the bolus injection of gadolinium after "wet taps." The findings of gadolinium accumulation in the cerebrospinal fluid (CSF) after *intravenous* injection in humans,[74,75] apparently without clinical symptoms, support the lack of or minimal sequela from the slow accumulation of gadolinium in the intrathecal space.

The possible mechanisms of gadolinium neurotoxicity and cell death include impairment of mitochondrial function, alterations in cell signal processes and signal transduction, and inhibition of cellular calcium hemostasis.[65] After intracisternal application in rats, the LD50s (μmol per kg) were noted to be lower for the macrocyclic GBCAs gadoteridol, gadoterate meglumine, and gadobutrol than the linear agents' gadodiamide and gadopentetate.[76] Despite their findings, the authors considered the margin of safety between a diagnostic dose and LD50 in humans to be very high, with a safety factor of 80.[76]

Encephalopathy and death after unintentional intrathecal injection of small doses of gadolinium are alarming. This is compounded by the preponderance of pain injections around the spine. This was the primary reason why the multi-specialty group developed a practice guideline.[35] The recommendations, as it pertains to encephalopathy after unintentional intrathecal injection, include:

The use of GBCA is contraindicated in subarachnoid (intrathecal) *interventional* pain injections.

Patients with an increased risk of intrathecal injection should be identified, including spinal stenosis, previous spine surgery, or kyphoscoliosis.

Because of the likelihood of unintentional intrathecal spread of gadolinium, a GBCA is recommended in epidural injections via an interlaminar approach.

Because of the likelihood of unintentional intrathecal spread of gadolinium, a GBCA is recommended for transforaminal epidural injections.

Suppose that gadolinium is necessary for an interventional pain procedure where there is a very low risk of possible unintentional intrathecal administration (e.g. lumbar sympathetic blocks, facet joint injections, medial branch blocks). In such cases, the low risk of intrathecal gadolinium administration should be adequately explained to the patient.

If gadolinium is considered essential to the pain procedure and injected near the epidural/subarachnoid space, measures should be taken to avoid advancing the needle tip into the subarachnoid space.

If gadolinium is employed, digital subtraction imaging guidance may be considered.

If there is a concern for unintentional intrathecal or subdural administration of a GBCA, appropriate radiographic imaging, such as MRI and CT, should be considered.

Differences Between Interventional Pain Procedures and Diagnostic MRIs and CT

In interventional pain procedures, small volumes are injected extravascularly and may be repeated after 1–3 weeks. These procedures are distinct from CT or MRI, in which large volumes of contrast are injected intravascularly. Most patients' medical issues have been identified and treated before they are referred to the pain clinic. Injections are not performed on an emergency basis because the patient's pain can be partially controlled with medications and other non-pharmacologic alternatives until the medical issue has been controlled or stabilized. These differences explain the PS and recommendations of the multi-specialty practice guidelines,[35] compared to the guidelines by radiology specialties.

Concluding Statements

The principles of radiation safety are outlined in this section. Although studies have shown that the accumulated radiation from interventional pain procedures is below the MPD, measures should be followed to minimize radiation exposure. The use of contrast media is essential in some interventional procedures. It appears that HRs to ICM and GBCAs are rare, probably because of the small doses employed and the extravascular route of injection. The clinical significance of gadolinium brain deposition/retention in the brain is unknown, and its occurrence after interventional pain procedures is very rare. The occurrence of NSF after pain is rare. Encephalopathy after unintentional intrathecal injection of gadolinium is an alarming development. Linear GBCAs are less stable, explaining the greater occurrence of NSF and gadolinium brain deposition with these agents than macrocyclic GBCAs. However, macrocyclic GBCAs have a higher incidence of HRs—although still lower than ICM—and have lower LD50s when injected intrathecally. These differences should be considered when deciding on the use of GBC. Since NSF and gadolinium brain depiction is less of a concern in interventional pain procedures, linear agents may be employed in perispinal injections. The availability of these agents is low, as some agents are withdrawn. Awareness of these adverse effects, shared decision making with patients, and observance of preventive measures to avoid these complications is paramount.

Key Points

- The biologic effects of ionizing radiation are proportional to the time of exposure, whereas radiation exposure is inversely proportional to the *square* of the distance from the radiation source.
- Modern fluoroscopy units typically employ ABC, which automatically adjusts kVp and mA to yield optimal brightness and contrast.
- The ICRP has produced estimates of the MPD of annual radiation to various organs. Exposure below these levels is unlikely to lead to any significant effects, but the ICRP recommends that workers should not receive more than 10% of the MPD.
- Continuous fluoroscopy for 1 min at 2 R per min was equivalent to the exposure during 130 chest radiographs.
- Practitioners using ionizing radiation should adhere to the ALARA principle ("As Low As Reasonably Achievable"), combining optimal techniques and shielding to minimize patient and personnel exposure.
- The x-ray tube should be positioned as far from the patient as possible without including unnecessary structures in the field of view.
- To minimize the dose to the patient, the largest field of view should be employed in conjunction with tightest collimation.
- Although protective lead gloves can reduce the exposure of the hands to radiation, they can produce a false sense of security.
- Leaded eyewear is recommended for practitioners who accumulate monthly readings on collar badges above 400 mrem (4 Sv).
- Digital subtraction electronically enhances the image, reducing the amount of CM needed by a factor of two to three times.
- The annual amount of radiation from interventional pain procedures is within the MPD.
- Of the common non-ionic monomers in clinical use, only iohexol and iopamidol are labeled for intrathecal use.
- The most common premedication regimen to reduce the risk of severe reactions to contrast media combines pretreatment with corticosteroids and antihistamines. However, the efficacy of steroid premedication is not consistent. Changing the ICM has been shown to decrease the breakthrough reactions.
- GBCAs have been used as alternatives to iodinated contrast agents in patients with known contrast allergies. This is because GBCAs have a lower incidence of overall and severe HRs compared to ICM.
- HRs are more common with macrocyclic ionic GBCAs and linear ionic GBCAs than with linear non-ionic GBCAs, partly because of their higher osmolality.
- In patients with previous HRs, a multi-specialty multi-society practice guideline recommended the use of a different iodinated CM and appropriate pretreatment.
- Macrocyclic GBCAs are more stable and dissociate less than linear GBCAs. The stability of the GBCA explains the more frequent occurrences of NSF and gadolinium brain deposition/retention with linear GBCAs than with macrocyclic agents.
- NSF is a systemic disease related to fibroblast formation enhanced by free dechelated gadolinium ions. It occurs mostly with linear non-ionic GBCAS followed by the linear ionic GBCAS; the lowest incidence occurs with the macrocyclic agents.
- For patients with renal insufficiency, a multi-specialty multi-society practice guideline recommends low-risk macrocyclic GBCAs and medium-risk linear ionic GBCAs. The smallest dose necessary to obtain clinical information should be used.

- Gadolinium brain deposition/retention in the brain occurs after repeated GBCA-enhanced MRI. This is mostly associated with linear GBCAs. Its occurrence is dose-related and not associated with kidney function. Its clinical sequelae have not yet been established.
- Gadolinium brain deposition/retention has not been reported after interventional pain procedures, partly because small extravascular doses are injected. Interventional pain physicians should be aware of the research developments in this area.
- An alarming development is encephalopathy after unintentional intrathecal injection of gadolinium. The volumes injected ranged from 1.5 to 5 mL of the GBCA. Macrocyclic GBCas have lower ED50s than linear GBCAs when injected intrathecally.
- A multi-specialty multi-society practice guideline issued Statements and recommended against intrathecal and transforaminal injections of GBCAs.

Acknowledgments

The material for radiation safety was originally prepared and published by Rathmell JP. *Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2012. I am grateful to Lippincott Williams & Wilkins, the original publisher, and Brian Brown, Executive Editor with Lippincott, for permitting the material to appear here in a modified format.

Suggested Readings

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Infection and Anticoagulation Considerations in Pain Procedures

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SECTION 1 RISK OF INFECTION IN INTERVENTIONAL PAIN PROCEDURES

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Introduction

Infections related to interventional pain procedures and implantable devices vary considerably based on the target location, causative pathogens, anatomic structures involved, collateral damage, and severity. Surgical site infections (SSIs) have been shown to significantly increase mortality, prolong hospital length of stay, and reduce health-related quality of life.[1–2] In addition, SSIs cost the United States healthcare system an estimated $3.5 to 10 billion dollars annually.[3] The total cost of a single spinal cord stimulator (SCS) infection has been estimated to range from $28,500 –$54,500 in the United States.[4]

Recently, there has been a global emphasis by national and international agencies and societies to create and promote recommended best practices to reduce SSI rates.[5–10] Despite these efforts, SSI rates have not significantly declined.[11] SCS infection rates are higher than those of other implantable devices, including cardiac pacemakers and total joint replacements.[11] An international survey of 506 physicians who performed SCS implants was conducted to examine compliance rates for the Centers for Disease Control and Prevention (CDC), National Institute for Health and Care Excellence (NICE), and Surgical Care Improvement Project (SCIP) infection control practice recommendations.[5,7,10] Only four of the 15 questions had compliance rates of ≥80%, thus further highlighting the need for physician education in the field. Both current infection rates for implantable pain devices and survey responses suggest a need for improved education for interventional pain physicians in infection control practices.

This section summarizes the literature and recommendations for commonly performed interventional pain procedures, with a distinction made between implantable device surgery including SCS and intrathecal drug delivery systems (IDDS) and non-implantable device procedures including epidural steroid injections, facet blocks, neuraxial and peripheral nerve blocks, joint injections, sympathetic blocks, radiofrequency, discography, and vertebral augmentation.

Definition of SSIs

Identification of SSI is based on physical examination findings of localized pain/tenderness, swelling, erythema, heat, or purulent drainage, cultures, and radiologic findings (Fig. 74.1).[5] Superficial SSIs involve the skin and subcutaneous tissues. Deep SSIs involve the fascia, muscle layers, and organ/space infections. Site infections occurring in the absence of an implantable device are defined as occurring within 30 days of the operation. When implantable devices are involved, the time is extended, and infections may occur within 12 months following a device implant.

Pathogens Associated With SSIs

Organisms that cause SSIs can be categorized as endogenous or exogenous sources. The most common pathogens are *Staphylococcus aureus*, *Staphylococcus epidermidis, Streptococcus*, *Escherichia*

• **Figure 74.1** A surgical site infection of a spinal cord stimulator generator site.

coli, and *Pseudomonas aeruginosa*. The most common source of infection is from the patient's own flora.[8,12,13] It has been shown that pathogenic *Staphylococcus aureus* isolated from an infected wound matches cultures from the patient's nares 80%–85% of the time.[14]

Scope of Interventional Pain Procedures and Risk of Infection

Interventional pain procedures and surgeries vary considerably based on the pain syndrome being treated, surgical technique, and surgical theater environment. The invasiveness of procedures varies, and thus different infection control practices must be considered. Recommendations to prevent SSIs have been published by the CDC, NICE, and SCIP (Tables 74.1, 74.2, and 74.3).[5,8,10,15]

Infection Rates

Despite an emphasis on reducing SSIs, the rate of infection has remained relatively stable over the past two decades. In the United States, approximately 500,000 SSIs occur annually, accounting for 17% of all nosocomial infections.[16] The relative risk of central nervous system infection following paraspinal injections has been estimated to be about 0.1%.[17] The risk of developing an epidural abscess from an indwelling catheter for postoperative analgesia has been reported to be 0.05%.[18] There have only been a few reports of infectious complications related to facet injections. Thus the true incidence is unknown.[19–24] Incidence of disc infection with discography has been estimated to be 0.15% per patient and 0.08% per disc injected.[25] Published systematic reviews on SCS and IDDS report infection rates ranging from 3.4%–12.4% and 2.4%–4.6%, respectively.[16,26-31]

Preoperative Risk Reduction

Patient Risk Factors

Physicians should recognize patient-related risk factors, including older age, poor nutritional status, diabetes mellitus, smoking, obesity, coexisting infection on a remote body site, colonization with *Staphylococcus aureus*, and altered immunity (e.g. immunosuppressive agents) prior to performing a procedure, and efforts should be made to correct any modifiable risk factors (Table 74.4).[32–35] Post-market surveillance data on SCS and IDDS implants revealed that 38% and 70% of patients with SCS and IDDS infections, respectively, have a medical comorbidity that increases the risk of infections.[12] Smoking has been associated with an increased risk of SCS infections, likely secondary to the development of microvascular disease leading to tissue ischemia and poor wound healing, and worse pain scores and opioid consumption post-SCS implant.[27,36–38] Although the biologic effects of cancer and chemotherapeutic drugs can weaken host immunity, a retrospective study demonstrated that implantable pain therapies can still be utilized in cancer patients without significantly increasing the risk of SSI when appropriate infection control measures are taken.[39]

A thorough history and physical examination should be performed preoperatively to identify patient risk factors prior to surgery. Many measures can be taken to reduce the risk of SSIs, such as glucose optimization, tobacco cessation (for at least four weeks), optimizing viral load in HIV patients, minimizing/avoiding perioperative steroids, and treating remote infections (e.g., urinary tract). Non-modifiable risk factors need to be documented, and a discussion with the patient regarding the associated increased risk of infection should occur prior to the pain intervention.

Staphylococcus Aureus Carriers

Staphylococcus aureus is the leading cause of SSIs, accounting for approximately 20% of all SSIs and 30% of ICD implant infection.[40–42] More than 80% of nosocomial *Staphylococcus aureus* infections are endogenous, and the number of cases of methicillin-resistant *S. aureus* (MRSA) SSIs is increasing.[5,43] Staphylococcus aureus nasal colonization rates range from 20%–50%.[44–48]

Methicillin-sensitive *S. aureus* (MSSA) and MRSA carriers have been shown to have a significantly higher risk of developing an SSI (two to nine times higher).[48–50] Therefore identification of carriers followed by decolonization is critical in reducing SSI rates, and is cost effective.[26,44,45,51–53] Prior to implantable pain therapies, patients can be screened for MSSA and MRSA. If positive, the patient can be decolonized, and preoperative antibiotic therapy is tailored based on the results.

Decolonization protocols involve the application of mupirocin 2% nasal ointment applied twice daily combined with chlorhexidine gluconate soap total-body washes daily for a duration of five days immediately preceding surgery.[44,54] Utilization of decolonization protocols in individuals colonized reduces the rate of postoperative infections by >50%.[44,56,56] No data exists to support the use of routine decolonization protocols in patients who are not found to be colonized with *S. aureus*.[49]

Antibiotic Prophylaxis

Preoperative antibiotic prophylaxis has been shown to significantly reduce the risk of SSIs, and the incidence of wound infection by approximately 50%, regardless of the type of surgery.[57] Antibiotic prophylaxis (Table 74.4) is recommended for implantable pain therapies (i.e. trials and implant stages). Proper antibiotic selection, route of administration, dosing, and timing are critical, as suboptimal implementation has increased the risk of infection by two- to six-fold.[58,59] Cephalosporins are recommended as first line agents. Clindamycin or vancomycin are alternative antibiotics if a patient has a β-lactam allergy. In individuals colonized with MRSA or at high risk for MRSA (e.g., institutions with a high rate of MRSA infections), vancomycin is recommended.[7,60] In individuals with vancomycin allergies, daptomycin may be considered.[61]

For effective antibiotic prophylaxis, minimum inhibitory concentrations must be reached prior to surgical incision and maintained throughout the duration of the surgery. Therefore weight-based dosing is critical. Preoperative antibiotics should be administered intravenously (IV) prior to breaching the skin (30–60 min or 120 min for vancomycin). Re-dosing is needed when the duration of surgery is longer than two half-lives of the administered antibiotic (Table 74.5).

The continuation of antibiotics in the postoperative period is not recommended beyond 24 h for clean surgical wounds. Prolonged antibiotic use in the postoperative period does not improve outcomes and may result in poorer outcomes.[62,63] Specifically, the continuation of antibiotics in the postoperative period has been associated with delayed normalization of body temperature and elevated C-reactive protein level.[62] The SCIP guidelines recommend discontinuation of antibiotics within 24 h of surgery.[7]

TABLE 74.1 Preoperative CDC, SCIP, NICE, and Author Recommendations for Reducing SSIs

Recommendations	CDC Evidence Rankings	SCIP Process of Care Performance Measures	NICE Guidelines	Authors' Additional Recommendations
• Identify and treat all remote infections.	IA			
• Identify patient risk factors				✓ [12,32–35]
• Optimize glucose control	IB			
• Discontinue tobacco use	IB			
• Require patients to shower or bath with an antiseptic agent prior to surgery.	IB			
• Preoperative screening and decolonization for SA carriers				✓ [43,44,51,53,54]
• Do not routinely use nasal decontamination for SA			✓	
• Appropriate selection of intravenous antibiotic prophylaxis based on hospital pathogens and type of surgery/procedure	IA	✓	✓	
• Weight-based antibiotic dosing				✓ [61,62]
• Appropriate prophylactic antibiotic received within one hour prior to surgical incision (two hours for vancomycin)	IA	✓	✓	
• Appropriate agent selection for skin antisepsis (povidone-iodine or chlorhexidine)	IB		✓	
• Vancomycin should not routinely be used	IB			
• Preoperative surgical scrub for at least 2–5 minutes using an appropriate antiseptic. Scrub the hands and forearms up to the elbows	IB		✓	
• Keep nails short and do not wear artificial nails	IB		✓	
• Sterile gown and gloves	IB			
• Do not wear hand or arm jewelry	II		✓	
• Do not use hair removal routinely	IA		✓	
• If hair is removed, use electric clippers immediately before surgery	IA	✓	✓	
• Evaluate for skin lesions or areas of local infection				✓
• Apply preoperative antiseptic skin preparation in concentric circles moving toward the periphery	II			
• Wide prep and drape	II			

CDC, Centers for Disease Control; *SCIP*, Surgical Care Improvement Projects; *NICE*, National Institute for Health and Clinical Excellence; *OR*, operating room; *SSI*, surgical site infection; *HEPA*, high-efficiency particulate arrestance

CDC Recommendation Ranking Categories:

IA: Strongly recommended for implementation and supported by well-designed experimental clinical or epidemiologic studies.

IB: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale.

II: Suggested for implementation and supported by suggestive clinical or epidemiologic studies or theoretical rationale.

There are no recommendations or evidence for the use of antibiotic prophylaxis in the majority of routine interventional pain procedures, i.e. such as epidural steroid injections and facet blocks. However, for procedures with a higher risk of infection (i.e. indwelling catheters, kyphoplasty, and device trials/implants), antibiotic prophylaxis is recommended.[5,8] For discography and other intradiscal procedures, controversy exists regarding the need for IV and/or intradiscal antibiotic administration.[8,64]

TABLE 74.2 Intraoperative CDC, SCIP, NICE, and Author Recommendations for Reducing SSIs

Recommendations	CDC Evidence Ranking	SCIP Process Care Performance Measures	NICE Guidelines	Authors' Additional Recommendations
• Wear a surgical mask in the OR if sterile instruments are exposed	IB			
• Wear a cap or hood to fully cover hair in the OR	IB			
• Wear two pairs of sterile gloves when there is a high risk of glove perforation and the consequences of contamination are high			✓	✓[87]
• Use sterile surgical gowns that are effective barriers when wet	IB		✓	
• If an incise drape is used, use an iodophor-impregnated drape			✓	
• Laminar flow and HEPA filters in OR	IB			
• Limit OR traffic	II		✓	
• Keep OR doors closed during procedure	IB			
• Adhere to principles of asepsis when placing spinal or epidural catheters	IA			
• Limit tissue trauma, maintain hemostasis, eradicate dead space, and avoid the electrocautery at tissue surface	IB		✓	
• Vigorous wound irrigation with bulb syringe				✓[99,101]
• Limit surgical time				✓[37,92]

Administration of intravenous antibiotics did not reliably achieve adequate intradiscal concentrations. Therefore only intradiscal antibiotics are recommended. However, *ex vivo* studies examining the effects of high antibiotic concentrations on cultured human intervertebral disc annular cells demonstrated deleterious effects on cell survival, cell proliferation, and metabolic rates; therefore these risks must be considered as well.[65]

Surgical Hand Washing

Appropriate surgical scrubbing of the hands and forearms is a CDC Category IB and NICE recommendation.[5,10] Commercially available antiseptic solutions in the United States contain alcohol, chlorhexidine, and/or povidone iodine. There is evidence that chlorhexidine-based scrubs reduce the number of colony-forming units (CFUs) compared to povidone-iodine scrubs. However, data supporting its clinical relevance are lacking. Therefore there is a lack of strong evidence to strongly support the use of one agent over another.[66] The duration of the surgical scrub appears to be the most important factor in ensuring adequate hand hygiene and limiting bacterial counts. Surgical hand washing lasting between 2 and 5 min results in statistically fewer CFUs than hand washing techniques of lesser duration.[67]

The removal of hand and wrist jewelry prior to surgical scrub is a CDC Category II and NICE recommendation as well as a recommendation by the American Society of Anesthesiologists and American Society of Regional Anesthesia and Pain Medicine (ASRA) when performing neuraxial procedures.[68] The presence of hand jewelry increases bacterial counts on the hands of healthcare workers even after hand washing.[5,10,15,69]

The method of hand hygiene required to minimize the risk of infections associated with interventional pain procedures has not been established. A full surgical scrub is recommended for implantable and indwelling catheters.

Appropriate Hair Removal

The CDC Category IA and NICE do not recommend removing hair routinely to reduce the risk of SSI, and if hair is removed, clippers should be used.[5,10] The timing and method of hair removal appear to be the most important factors to consider. A meta-analysis examining hair removal techniques concluded that there was no difference in SSI rates when comparing no hair removal to hair removal with chemical or clipper methods. However, shaving methods increase the risk of SSIs.[70] Both clipping and shaving hair 24 h or more before an operation significantly increases the risk of SSI.[5,71,72]

Intra-procedural Risk Reduction

Patient Skin Preparation in the Operating Room

Antiseptic solutions containing isopropyl alcohol, povidone iodine, and chlorhexidine gluconate are most commonly used for skin preparation in patients. Prior to applying a skin antiseptic, gross contamination around the incision site should be removed (CDC Category IB).5 A randomized controlled trial and meta-analyses have shown that chlorhexidine significantly reduces the rate of SSIs and results in cost savings in comparison to povidone iodine.[73–75]

TABLE 74.3 Postoperative CDC, SCIP, NICE, and Author Recommendations for Reducing SSIs

Recommendations	CDC Evidence Ranking	SCIP Process of Care Performance Measures	NICE Guidelines	Authors' Additional Recommendations
• Prophylactic antimicrobial discontinued within 24 hours of surgery		✓		
• Occlusive dressing for a minimum of 24 to 48 hours	IB		✓	
• Do not routinely use topical antimicrobial agents for surgical wounds that are healing by primary intention			✓	
• Continued comorbidity optimization				✓
• Close postoperative wound surveillance				✓ [27]
• When SSI is suspected, prescribe an antibiotic that covers the likely causative organisms. Consider local resistance patterns and the results of microbiological tests in choosing an antibiotic.			✓	
• Consult an infectious disease specialist if any sign or warning signals of infection are present				✓ [163,164]
• Wash hands before and after dressing changes	IB			
• Use sterile technique for dressing changes	II		✓	
• Educate patient and family on proper incision care, symptoms of SSI, and importance of reporting symptoms	II		✓	

For interventional pain procedures, the United States Food and Drug Administration has not approved the use of chlorhexidine for neuraxial procedures because of the lack of clinical safety trials. However, the use of chlorhexidine for spinal anesthesia has not been shown to increase neurologic complications.[76] The use of chlorhexidine prior to epidural catheterization has been shown to be superior to povidone iodine in reducing catheter colonization rates.[77] Although there are no studies directly comparing infection rates with the use of chlorhexidine gluconate versus povidone iodine for interventional pain procedures, based on extrapolation of data from other surgical subspecialties, chlorhexidine-based products may offer improvements in infection control rates.

TABLE 74.4 Patient-Related Risk Factors for Surgical Site Infection

Older age
Poor nutritional status
Diabetes mellitus
Smoking
Obesity
Coexisting infections at a remote body site
Colonization with *Staphylococcus aureus*
Altered immune status

Modified from Mangram et al. 1999.[5]

Draping

Iodophor impregnated drapes may reduce the number of positive post-procedural skin cultures.[78–80] However, there are no data to support their routine use for the reduction of SSIs.[81,82] While the use of iodophor impregnated drapes may be considered for high risk patients, the literature does not support universal usage.

Surgical Attire

Maximal sterile barrier precautions (surgical cap, mask, and sterile gloves and gowns) for surgical procedures are recommended by the CDC (Category IB), NICE, and SCIP. In 2004, the CDC and Healthcare Infection Control Practices Advisory Committee released a statement recommending the use of face masks for neuraxial procedures after eight cases of bacterial meningitis following neuraxial procedures were linked to practitioners who were not wearing masks.[83]

Sterile gloves are recommended for interventional pain and implantable therapies. While there are no studies directly comparing the risk of SSIs with single versus double gloving techniques, double gloving has been shown in multiple studies to reduce the

TABLE 74.5 Prophylactic Antibiotic Recommendations

Antibiotic	Standard Intravenous Dosing	Timing Prior to Incision	Redosing Interval	Indications
Cefazolin	1 g ≤ 80 kg 2 g > 80 kg 3 g > 160 kg	Within 30–60 min	3–4 h (CrCl > 50 mL/min) 8 h (CrCl 20–50 mL/min) 16 h (CrCl < 20 mL/min)	1) First-line
Clindamycin	600 mg ≤ 80 kg 900 mg > 80 kg 1200 mg > 160 kg	Within 30–60 min	6 h (CrCl > 50 mL/min) 6 h (CrCl 20–50 mL/min) 6 h (CrCl < 20 mL/min)	1) β-lactam allergy
Vancomycin	1 g ≤ 80 kg 2 g > 80 kg 3 g > 160 kg	Within 120 min	8 h (CrCl > 50 mL/min) 16 h (CrCl 20–50 mL/min) None (CrCl < 20 mL/min)	1) β-lactam allergy 2) Known methicillin-resistant *S. aureus* colonization

Modified from Bratzler et al. 2004 and Alexander et al. 2011[60,62]

number of inner glove perforations.[84] Glove perforations result in higher surgical infection rates. Therefore double gloving should be considered for implantable device surgeries to reduce the risk of SSI and protect the practitioner.

Surgical Technique and Procedural Efficiency

Appropriate surgical training and efficiency have also been shown to help reduce SSIs. Inadequate physician experience, low procedural volumes, and extended operative times have been suggested as possible risk factors for SSIs.[85–87] A retrospective review of IDDS and SCS implants for cancer patients suggested that extended operative times may be a risk factor for SSIs.[39] Therefore an attempt should be made to limit surgical time.[26] In addition, recent survey data for SCS demonstrated an inverse relationship between procedural volume and operative times.[88]

Wound Irrigation

The efficacy of wound irrigation depends on the delivery method, volume, type of solution, and additives delivered. Controversy exists regarding the use of high-pressure and low-pressure pulsatile lavage as they may result in the deep seeding of bacteria into exposed tissues and impaired wound healing.[89] There is no consensus on the optimum volume of irrigation to use. However, animal studies suggest that larger volumes are superior.[90]

Irrigation solutions typically consist of normal saline, detergents, or antibiotics. Bacitracin solution has not been shown to be superior to normal saline in reducing the presence of wound bacteria.[91,92] However, both benzalkonium chloride and bacitracin have been associated with impaired wound healing.[92,93] If wound irrigation is performed for implantable therapies, it is recommended to use normal saline through a bulb syringe.[94]

Topical Antimicrobials

Topical antimicrobials for SSI prophylaxis have been studied in the form of impregnated dressings, topical powders, and device envelopes. Randomized controlled trials using chlorhexidine impregnated dressings for epidural catheters have shown a greater than seven fold reduction in catheter-site bacterial colonization with a mean catheter duration of 3.6 days.[95–97] The use of chlorhexidine impregnated dressings should be strongly considered in any procedure where a catheter/lead is left exposed for an extended period in a patient at high risk for SSI (i.e. SCS trials, IDDS catheter trials, indwelling epidural catheters).

Intrasite vancomycin powder has gained popularity, specifically in spine surgery.[98] However, the FDA does not currently approve its use. The reported efficacy of vancomycin powder for SSI reduction is conflicting.[99–105] Meta-analyses and systematic reviews suggest that intrasite application of vancomycin powder is effective in preventing SSIs, specifically when hardware is implanted.[106–109] Furthermore, animal studies have demonstrated a reduction in SSI at the implant site with local vancomycin.[110] However, there is concern that intrasite vancomycin may increase the risk of seroma formation, which can impair wound healing. In addition, it may increase the incidence of gram-negative and polymicrobial SSIs.[111] Further studies are warranted to support the routine use of vancomycin powder for implantable pain therapies.

An antimicrobial envelope is a bio-absorbable polypropylene mesh that releases antibiotics. An antimicrobial envelope containing minocycline and rifampin has been shown to reduce ICD infection rates by 60% when used empirically and by more than 87% when used selectively in patients considered at high risk for SSI.[112–114] There is currently no specific data to support its use in SCS and IDDS implants. However, its use could be considered in patients at a high risk of SSI.

Operating Room Environment

Ventilation and OR traffic likely affect SSI rates. Laminar-flow ORs and high-efficiency particulate air filters have been shown to reduce SSI and wound contamination compared to conventional airflow systems.[115–117]

Personnel are the major source of contamination in the OR.[118] The number of personnel and traffic flow rates in the OR positively correlate with the degree of airborne contamination.[119] Education, preoperative planning, communication, and limiting surgical time are the most effective measures to decrease traffic flow.

There are many potential sources of contamination from equipment within the OR (i.e., light handles, fluoroscopic C-arm, and ultrasound probe). Contamination of sterile light

handles has been reported to be as high as 14.5%. Therefore the handling of OR lights should be minimized.[118,120] Biswas et al. evaluated the sterility of 25 C-arm drapes placed with the aseptic technique after their use during spine surgery.[121] All locations were contaminated at the end of the surgical case. The front, top half, and superior end of the image intensifier were associated with highest contamination rates. All OR personnel should avoid contact with the C-arm.

Wound Closure

It is important to minimize dead space during wound closure, which allows for the accumulation of serous fluid and blood, serving as a medium for bacterial growth. Layered closure techniques also help minimize dead space and tissue tension, which also promotes wound healing.[122] Certain suture types and materials are thought to promote bacterial colonization. For example, multifilament sutures (i.e. silk and vicryl) may promote bacterial colonization between filaments. However, there is a lack of evidence to support the use of one type of suture to reduce SSI.[123,124]

There is conflicting evidence on the benefit of the closure method (suture vs. staples).[125] A meta-analysis of randomized controlled trials in obstetrics/gynecology, general, head/neck, and vascular operations suggested that staples were associated with significantly fewer SSIs.[126] A Cochrane review concluded insufficient evidence to suggest a difference in SSI rates when comparing suture versus staple closures for leg wounds after vein graft harvesting during cardiopulmonary bypass surgery.[127]

Needle Contamination

Needle contamination occurs despite adequate skin preparation. Epidural needle contamination rates have been reported to be as high as 35% despite adequate skin preparation with 10% povidone iodine.[128] Higher rates of discitis following discography using a non-styleted, single-needle technique than a styleted,

TABLE 74.6 Case Reports of Contaminated Ultrasonography Coupling Gel Causing Nosocomial Infection

Author	Gel Used	Antimicrobial Agent	Identified Microorganism	Source of Contamination	Associated Procedure	Type of Nosocomial Infection
Chittick, P. et. al.[148]	Other-Sonic; Pharmaceutical Innovations, Inc., Newark, NJ	Not indicated	*Pseudomonas aeruginosa*	In-use and unopened gel bottles	Transesophageal echocardiography	Respiratory tract infection
Olshtain-Pops, K. et. al.[140]	250 mL un-identified gel bottle	Not indicated	*Achromobacter xylosoxidans*	250 mL in-use gel bottles	Transrectal prostate biopsy	Bacteriuria and septicemia
Marigliano, A. et. al.[144]	not indicated	Methylchloroisothiazolinone and methylisothiazolinone	*Burkholderia cepacia*	Not indicated	Echocardiographic procedures	not indicated
Jacobson, M. et. al.[137]	250 mL gel bottles from 4 un-identified manufacturers	Propyl and methyl parabens	*Burkholderia cepacia, Klebsiella oxytoca, Stenotrophomonas maltophilia, Ralstonia pickettii, Pantoea agglomerans, Enterobacter ictaluri, Burkholderia stabilis*	250 mL in-use gel bottles	Diagnostic ultrasonography	Respiratory tract infection, bacteriuria, skin wound
Hutchinson, J. et. al.[139]	250 mL un-identified gel bottles, 5 L opened stock bottles	Methyl Paraben	*Burkholderia cepacia, Enterobacter cloacae*	Intrinsically contaminated gel during the manufacturing process	Transrectal prostate biopsy	Urinary tract infection and septicemia
Weist, K. et. al.[142]	500 mL un-identified gel bottle	Not indicated	Methicillin-susceptible *Staphylococcus aureus*	Dispensing spatula and 500 mL in-use gel bottle	Neonate hip-joint sonography	Pyoderma
Gaillot, O. et. al.[138]	250 mL Sonecho gel bottles; Echos Contacts, Eragny, France	Not indicated	*Klebsiella pneumoniae* producing extended-spectrum β-lactamase	Wide-mouthed bulk container	Emergency Room ultrasound scan	Urinary tract infection and skin lesion
Keizur, J. et. al.[149]	Not indicated	Not indicated	*Pseudomonas cepacia*	Portable dispensing bottles and opened bulk dispensers	Transrectal prostate biopsy	Urinary tract infection

Used with permission from Provenzano et al. 2013.[147]

TABLE 74.7 Guidelines for Infection Control Practices for Ultrasound-guided Procedures

- Follow the Centers for Disease Control and Prevention's guidelines for disinfection and sterilization in healthcare facilities for reprocessing ultrasound transducers.
- Prior to performing ultrasound scanning, confirm that the equipment was cleaned and disinfected appropriately.
- Use a sterile ultrasound sheath or sterile adhesive transparent dressing.
- Single-dose sterile ultrasound transmission gel should be used for the following procedures:
  1. Performing a biopsy or puncture
  2. Procedures involving mucous membranes
  3. Scanning non-intact skin
  4. Scanning near a surgical wound
  5. Scanning neonates and critically ill pediatric patients
- Non-sterile ultrasound gel may be used for low-risk, non-invasive procedures on intact skin and for low-risk patients.
- Seal multidose, non-sterile gel containers and replace when empty.
- Do not reuse ultrasound gel containers and replace when empty.
- When warming ultrasound gel, dry heat is the preferred method.

Modified from Oleszkowicz et al. 2012 and Narouze et al. 2012.[142,147]

double-needle technique (1.4% versus 0.4% per disc) have been reported.[13] Styleted needles should be used for all neuraxial procedures to reduce the risk of needle coring, which can introduce skin bacteria into the injection site. A double-needle technique should be considered intradiscal procedures. For discography, minimizing intradiscal needle time has also been suggested to reduce the incidence of discitis.[129]

Ultrasound Guided Regional Anesthesia and Pain Procedures

Both the ultrasound gel and probe can serve as vectors for infection (Table 74.6). Individuals performing ultrasound guided regional anesthesia and pain procedures should try to minimize infection and cross-contamination through the ultrasound gel and probe.

Contaminated ultrasound gel has been implicated in several nosocomial infections, which led to an FDA safety communication calling for the use of sterile ultrasound gel for transthoracic echocardiography.[130–137] Guidelines by Health Canada were published in 2004 recommending the use of sterile gel in all procedures that pass a device through tissue.[138] Recently, in the United States, recommendations based on expert opinions have been proposed to minimize clinical risk (Table 74.7).[134] These recommendations are based on the Health Canada recommendations recommending the use of single-use sterile gels for invasive procedures involving neonates, for all procedures involving sterile equipment or non-intact skin, and for procedures involving mucous membranes. In addition, several expert opinion publications have recommended the use of sterile gel for all interventional pain procedures.[134,139–142] Non-sterilely packaged ultrasound gel typically contains parabens. However, antimicrobial resistance to parabens has been described, and bacterial and fungal contamination of ultrasound gel packaged in bottles has been shown to be present prior to patient use.[140] Single-use, sterile ultrasound gel packets are recommended for use in interventional pain and regional procedures.[141]

Ultrasound equipment can also serve as a potential vector for nosocomial infection.[143–145] While there are no data evaluating the efficacy of sterile probe covers or adhesive transparent dressings for reducing procedure infection rates, their use is recommended for interventional pain and regional anesthesia procedures.[139]

The risk of infection is low when appropriate steps are taken. A retrospective review evaluating 7476 patients who received an ultrasound guided single injection peripheral nerve blockade using a low-level disinfection technique combined with a sterile transparent film barrier dressing to cover the ultrasound transducer and sterile ultrasound gel demonstrated no indications of block-related infections.[146]

Medication Vials

The misuse of single-use vials (SUVs) for multiple patients has resulted in outbreaks of *Staphylococcus aureus* infections. In 2012, the CDC issued a statement emphasizing the importance of proper usage of SUVs because of an outbreak of *Staphylococcus aureus* infections in 10 patients treated with interventional pain procedures.[147] The final recommendations were 1) contents of an SUV should be withdrawn using a sterile syringe in an aseptic manner; 2) contents should be used promptly; 3) the vial and any remaining contents should be disposed of; 4) SUVs should not be used on multiple patients; 5) if SUVs are used on multiple patients, the medication should be separated only from an unused SUV into SUV or syringes by qualified healthcare personnel under a laminar flow hood using strict adherence to the *United States Pharmacopeia* 797 standards.[148]

Postoperative Risk Reduction

Wound Dressings

The CDC and NICE recommend the use of sterile occlusive dressings for 24–48 h for incisions closed by primary intention (Category IB).[5] Early studies suggested that occlusive dressings augment wound healing and decrease the rate of SSI.[149,150] There is currently insufficient evidence to support any type of wound dressing to reduce SSI rates.[151,152]

Patient Education and Postoperative Wound Surveillance

During the postoperative period, the optimization of medical comorbidities should continue, including tobacco cessation and glucose control. Patients and family members should be educated on signs and symptoms of an emerging SSI, incision care, and the importance of reporting any signs of infection. Patients should be seen within 10–14 days of surgery to evaluate for appropriate wound healing and signs of SSI, and any dressing changes should

be done using a sterile technique.[26] Any evidence of a developing SSI requires closer follow up.

Infection Management

Prompt identification is the most important step in the appropriate management of SSI. Laboratory tests, such as white blood cell (WBC) count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), can aid in the identification process. It is common for WBC, ESR, and CRP values to rise transiently in the postoperative period because of the appropriate perioperative inflammatory response. CRP levels rise 4–6 h after acute tissue injury, peaking around the second or third postoperative day following total joint arthroplasty and spine surgery.[153,154] ESR levels rise more slowly, peaking around the fourth or fifth postoperative day. C-reactive protein also returns to normal more rapidly (14–21 days) and predictably compared to ESR.[154,155] Postoperative CRP kinetics are more responsive to and predictive of infection.[154] Therefore failure of CRP levels to normalize or an unexpected rise in CRP is a highly sensitive predictor of an SSI. Likewise, a normal CRP level is highly specific for the lack of an SSI.

If any purulent drainage is identified, samples should be sent for culture and sensitivity. Imaging is often recommended for neuraxial procedures and implantable pain therapies to determine if an infection exists in the epidural space. Magnetic resonance imaging with and without gadolinium is the imaging modality of choice, but device MRI conditionality must be considered.[156]

Sometimes, superficial infections can be managed with wound care and antibiotics, but implantable device infections often require explants.[157] When the device is removed, all hardware should be sent for culture and sensitivity. The formation of biofilms makes eradication of an infection involving hardware exceedingly difficult. Relapse of infection has been reported to occur in over half of patients with ICDs left in place when generator pocket infections were identified.[158] Similarly, conservative management of deep brain stimulator infections is successful in less than 40% of cases.[159] Specifically for SCS SSIs, a multicenter retrospective review demonstrated that explantation was required in approximately 78% of patients.[157] Re-implantation should only be considered when the complete resolution of the infection is established, and an alternative site for the IPG or pump reservoir site should be considered.

Conclusion

Surgical site and procedural infections are associated with significant morbidity, clinical consequences, and economic costs. Physicians performing interventional procedures must understand and implement appropriate infection control guidelines. Tables 74.8 and 74.9 provide summary infection control recommendations based on the pain procedure classification. When infections occur, prompt recognition and appropriate treatment are required. In addition, further research is warranted specifically for interventional pain procedures to further define the guidelines and recommendations.

TABLE 74.8 Pain Procedure Classifications to Guide Infection Control Measures

A	B	C	D	E
Trigger point injections	Interlaminar epidural steroid injections	Intradiscal procedures	Peripheral nerve stimulation trials	Peripheral nerve stimulation implants/ revisions
Peripheral nerve blocks	Transforaminal epidural steroid injections	Indwelling catheters (peripheral, epidural, intrathecal)	Spinal cord stimulation trials	Spinal cord stimulation implants/revisions
	Facet joint and medial branch nerve block injections and radiofrequency ablation		Dorsal root ganglion stimulation trials	Dorsal root ganglion stimulation implants/ revisions
	Musculoskeletal and joint injections		Vertebral augmentation (vertebroplasty and kyphoplasty)	Interspinous spacer/ fusion implants/revisions
	Sacroiliac joint injections and sacral lateral branch blocks		Minimally invasive lumbar decompression	Intrathecal catheter and pump implants/revisions
	Paravertebral blocks		Basivertebral nerve ablation	Sacroiliac joint fusion
	Sympathetic blocks (stellate, ganglion impar, splanchnic, celiac, lumbar, superior hypogastric)			
	Single shot intrathecal drug trials			
	Intrathecal pump refills			

C, Cervical; *L*, lumbar; *S*, sacral; *T*, thoracic.

TABLE 74.9 Surgical Site Infection Risk Reduction Technique Summary of Recommendations Based on Procedure Type

Risk Reduction Techniques[#]	A	B	C	Implantable Therapies
Identification and optimization of patient risk factors	x	x	x	x
S. aureus screening and decolonization for carriers			Implantable trials*	x
Pre-procedural intravenous antibiotics			x	x
Hand washing with soap and water or an alcohol-based hand rub	x	x	x	x
2–5 minute surgical hand scrub			x	x
Do not wear hand or arm jewelry		x	x	x
Sterile gloves	x	x	x	x
Double gloving				x
Sterile surgical gown			x	x
Surgical cap and mask		x	x	x
Patient skin antisepsis with chlorhexidine	x	x	x	x
Full length body drape			x	x
Use of styleted needle		x	x	x
Sterile C-arm cover			x	x
Sterile ultrasound probe cover and gel	x	x	x	x
Wound irrigation with sterile saline				x

*Only recommended for consideration for implantable pain therapy trials.

[#]Refer to Table 74.8 for procedure classification.

SECTION 2 ANTICOAGULATION CONSIDERATIONS IN INTERVENTIONAL PAIN PROCEDURES

Honorio T. Benzon

Introduction

The American Society of Regional Anesthesia and Pain Medicine (ASRA) published several guidelines on regional anesthesia in patients on anticoagulants,[1] including the occurrence of spinal hematoma after epidural steroid injections or SCS placements when the regional anesthesia guidelines were adhered to or when the coagulation studies were normal led ASRA to create another guideline specifically for interventional pain procedures.[2,3] The reasons for these occurrences include pain in elderly patients, spinal stenosis with diminished epidural space, or scarring after laminectomy with scarring. SCS placement involves the use of large-bore needles with several advancements and retractions to optimally place the electrodes. Pain clinic patients may also be on medications usually considered not to affect hemostasis but may impede clotting. These drugs include anti-convulsants and selective serotonin reuptake inhibitors (SSRIs).[4,5] This section will deal with interventional pain procedures in patients on anticoagulants. The GPIIB inhibitors will not be discussed because they are administered for a short period, and the patients are usually maintained on P2Y12 antiplatelet inhibitors.

Stratification of Risks

The ASRA pain guidelines stratified the risk of bleeding according to the type of interventional procedure (Table 74.10). The risks of bleeding, progression, and consequences of hematoma vary with different procedures. For example, the abdominal and pelvic sympathetic blocks are close to large vascular structures, cannot be easily compressed, and symptoms associated with hematoma from these injections are vague. Intravertebral procedures are associated with compression of the spinal cord, with devastating consequences. Trigger point injections, superficial nerve blocks (e.g. occipital nerve blocks in the scalp), and joint injections are in avascular areas and are associated with minor bleeding complications. Mild anticoagulation is probably acceptable when the risk and consequences are small to prevent the patient from having a stroke, myocardial infarction, or venous thromboembolism (VTE).

Patients at high risk for bleeding undergoing low-or intermediate risk procedures should be treated as intermediate or high risk, respectively. Patients with a high risk for bleeding include the elderly, concurrent use of anticoagulants, low body weight, or advanced liver and renal disease.

TABLE 74.10 Pain Procedures According to the Potential Risks for Serious Bleeding

High Risk Procedures	Intermediate Risk Procedures	Low Risk Procedures
SCS trial and implant	Interlaminar and transforaminal ESIs	Peripheral nerve blocks
IT catheter and pump implant	Cervical facet MBB and RFA	Peripheral nerve stimulation
Vertebroplasty, kyphoplasty	Intradiscal procedures	Pocket revision, IPG, and IT pump replacement
Epiduroscopy and epidural decompression	Sympathetic blocks (stellate, lumbar, visceral)	Thoracic and lumbar facet MBBs and RFA
Percutaneous decompression laminotomy	Trigeminal and sphenopalatine ganglia blocks	Sacroiliac joint injections and LBBs
Dorsal root ganglion stimulation		Peripheral joints and musculoskeletal injections
		Trigger point and piriformis injections

ESIs, Epidural steroid injections; *IT*, intrathecal; *IPG*, implantable pump generator; *LBB*, lateral branch block; *MBB*, medial branch block; *RFA*, radiofrequency ablation.

From Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anesthesia and Pain Therapy, the American Academy of Pain Medicine (AAPM), the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med.* 2018;43:225-262 (with permission).

Aspirin and Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin irreversibly inactivates COX-1 through the acetylation of the amino acid serine, blocking thromboxane production and inhibiting platelet activation, platelet aggregation, and thrombosis.[6] The drug inactivates the COX-1 isoenzyme in the bone marrow megakaryocytes, which are responsible for the production of platelets. Aspirin also impairs secondary hemostasis and stability of the thrombus by acetylating fibrinogen and enhancing fibrinolysis.[7] At higher doses, aspirin prevents endothelial cell prostacyclin production by inhibiting COX-2.

Low dose aspirin, up to 100 mg, has been recommended by several United States guidelines for the primary prevention of cardiovascular disease in the elderly.[8,9] Recent studies have questioned this practice. While one large study showed a small but statistically significant benefit, the improvement was seen primarily in the first five years and mostly in diabetic patients.[10] The salutary effect was not duplicated in six other trials.[8]

A recent publication compared the clinical efficacy of aspirin with warfarin, heparin, dabigatran, and rivaroxaban in preventing VTE after total hip replacement (THR) and total knee replacement (TKR).[11] A separate analysis of the THRs and TKRs showed no statistically significant difference in VTE risk and pulmonary embolism (PE) between aspirin and the other anticoagulants. The risk of adverse events, including major bleeding, was also not statistically different.[11] In addition, and aspirin had a VTE risk not statistically significantly different from low molecular weight heparin (LMWH). These conclusions support the endorsement by the American College of Chest Physicians (ACCP) that aspirin is used in VTE prophylaxis after THR and TKR.[12]

Peak levels occur 30 min after aspirin ingestion, and significant platelet inhibition is present at 1 h.[13] For enteric-coated aspirin, peak plasma levels may be delayed until 3–4 h after ingestion. The average life span of a platelet is 7–10 days.[14] Approximately 10% of the circulating platelet pool is replaced every day,[15] resulting in 50% of the circulating platelets not affected by aspirin at five days.

The patient can continue to take aspirin when low risk pain procedures are performed.[3] While the regional guidelines permit neuraxial injections in the presence of aspirin, the pain guidelines do not. The length of discontinuation depends on the reason for the patient to be on aspirin: six days for primary prevention (aspirin in patients with no overt cardiovascular disease) and four days for secondary prophylaxis. The drug was resumed 24 h after the procedure (Table 74.11).

Phosphodiesterase (PDE), dipyridamole, and cilostazol hinder PDE isoenzymes expressed by platelets. PDE-3 inhibitors increase the levels of secondary messenger cyclic adenosine monophosphate (cAMP), while PDE-5 inhibitors increase cyclic guanosine monophosphate (cGMP) levels. Cilostazol inhibits PDE-3, while dipyridamole inhibits PDE-3 and PDE-5; dipyridamole has been combined with aspirin for a more pronounced effect. By blocking cAMP, cGMP, and PDEs, these drugs reduce platelet aggregation by approximately 40%[16]; they also increase vasodilatation. Dipyridamole had a half-life of 10 h. The extended-release dipyridamole, used in combination with aspirin, has a half-life of 13.6 h.[17] Cilostazol reaches peak plasma concentrations at 2 h. Maximum platelet aggregation occurs at 6 h.[16] Similar to dipyridamole, cilostazol has an elimination half-life of 10 h. Five half-lives, where 97% of the drug is eliminated,[18] is equivalent to 50 h. Stopping the drugs for two days should be adequate, with the safe resumption of the drugs occurring 24 h after the procedure.

NSAIDs reversibly blocked COX. Five half-lives resulted in a discontinuation period of 1–2 days for ibuprofen, diclofenac, ketorolac, and indomethacin, four days for naproxen and meloxicam, six days for namebutone, and ten days for oxaprozin and piroxicam. The drugs were resumed one d after the procedure.

P2Y12 Inhibitors

ADP released from platelet dense granules binds to two platelet G-protein-coupled receptors, $P2Y_{1,}$ and $P2Y_{12}$ receptors. $P2Y_1$ initiates ADP-induced platelet aggregation, while $P2Y_{12}$ facilitates platelet aggregation by inhibiting the adenylate cyclase-mediated signaling pathway and decreasing intracellular cAMP levels. P2Y12 inhibitors include clopidogrel, prasugrel, ticagrelor, and cangrelor. Patients with cardiovascular problems are usually prescribed a combination of a P2Y12 inhibitor and aspirin, known

TABLE 74.11 Recommended Intervals between Stoppage and Resumption of the Antiplatelet Medications and Medium and High Risk Pain Procedures

Drug	The Interval Between Discontinuation and Pain Procedure	Resumption of the Drug
Aspirin	Four for secondary prophylaxis, six for primary prophylaxis	24 h
Cilostazol	Two days	24 h
Dipyridamole	Two days	24 h
Clopidogrel	Seven days, five days if platelet function studies show adequate recovery	12 h when loading dose is given, 24 h for the usual maintenance daily dose
Prasugrel	Seven days	24 h
Ticagrelor	Five days	24 h
Cangrelor	1–2 h	[a]

[a]Patients who are administered cangrelor are usually maintained on oral P2Y12 inhibitors.

as "dual antiplatelet therapy." After percutaneous coronary intervention and an initial period of short-term dual therapy, monotherapy with a P2Y12 inhibitor appears to be a superior strategy in terms of balancing bleeding and thrombotic risks after PCI.[19]

Clopidogrel and prasugrel are irreversible P2Y12 inhibitors. Both are pro-drugs that require two-step metabolism to be converted to their active metabolites. Clopidogrel is susceptible to genetic polymorphisms, and 9% of patients do not respond to the drug. Clopidogrel causes 60% inhibition of platelets, while prasugrel results in 90% inhibition.[20] For this reason, a seven day stoppage is recommended for medium and high risk procedures (Table 74.11). One study showed that most patients had no platelet inhibition after five days, while the rest had minimal inhibition.[21] A five day period may be reasonable in patients at high risk for VTE or cardiac events and scheduled for an SCS trial. This is prescient because a trial occurs over 5–7 days. Platelet activity should be tested in cases with a five day stoppage. The commonly used tests of antiplatelet activity of P2Y12 receptors include either the VerifyNow P2Y12 assay or the platelet mapping portion of thrombelastography.

Ticagrelor, in contrast to clopidogrel and prasugrel, is a direct-acting P2Y12 inhibitor. It inhibits the aggregation of platelets by 90%; platelet function recovery is adequate five days after stopping the drug.[22] Cangrelor, another direct P2Y12 inhibitor, is administered intravenously and is approved for clinical use in patients undergoing percutaneous coronary intervention.[23] Cangrelor has a fast onset of a few minutes and a half-life of 3–7 min. Platelet function was normalized 1 h after it was stopped. If a pain procedure is necessary, at least a 1 h interval should be observed.

Prasugrel and ticagrelor should be resumed 24 h after the procedure, as these drugs take effect within 2–4 h. If given in its usual 75 mg dose, clopidogrel can be started 12 h after the pain procedure since it takes one or two days to reach full effect. However, a 300–600 mg loading dose of clopidogrel takes effect after a few hours and should be started 24 h later.

Two novel P2Y12 receptor antagonists are currently in clinical development. Vicagrel is an analog of clopidogrel that enhances the formation of its active metabolite. Orally administered, the time to peak effect is 4 h, while the offset takes 5–10 days, similar to clopidogrel.[24] Selatogrel is injected subcutaneously, has a rapid onset, and the offset is approximately 24 h. The appropriate clinical doses of vicagrel and selatogrel are yet to be determined.

Vitamin K Antagonists

Warfarin inhibits γ-carboxylation of vitamin K-dependent coagulation factors. These clotting factors (CF) have different half-lives: 6–8 h for CF VII, 20–24 h for CF IX, 20–42 h for CF X, and 48–120 h for CF II.[25,26] The initial anticoagulation results from inhibition of clotting factor VII. This effect is antagonized by a reduction in anticoagulant protein C, making the international normalized ratio (INR) unreliable during the early phase of warfarin therapy. The full anticoagulant effect of warfarin does not occur until four days later when the levels of factor II are significantly decreased. Concentrations of CFs of 40% or more are considered adequate for hemostasis; levels below 20% are associated with bleeding.[27] Whereas warfarin is used in the United States, acenocoumarol is prescribed in Europe. The difference is the normalization of the INR between the two drugs: five days for warfarin and three days for acenocoumarol.

Warfarin has a narrow therapeutic index, wide interpatient dosing variability, and genetic factors account for variations in dose requirements. Patients with variations in CYP2C9 and/or VKORC1 enzymes require lower doses of warfarin. However, studies on genetic-based dosing have not been uniform in their findings,[28] and comparisons with validated dose-response nomograms have not been adequately studied, and pharmacogenetic testing is not cost effective.[29]

For patients who require emergency surgery (within 4 h of the decision to operate), the American College of Cardiology and the American College of Chest Physicians recommend 4-factor prothrombin complex concentrates (PCCs) for reversal of vitamin K antagonists.[30,31] Concurrent administration of vitamin K is advised to allow for the liver synthesis of clotting factors since the CFs in PCC have short half-lives, ranging from 6–72 h.[31] Interestingly, a study of American Society of Anesthesiology members preferred to administer fresh frozen plasma instead of the FFP.[32]

In patients who have not taken warfarin, an INR of 1.4 is acceptable for neuraxial injections. This is because studies have shown that the activities of vitamin K-dependent CFs are adequate at this INR level. In patients who discontinued warfarin, usually for five days, the ASRA guidelines recommend normalization of the INR (1.2 or less) before medium and high risk procedures are performed (Table 74.12).[3] This recommendation is supported by a study that showed the levels of CF X and II to be below 40%

in two patients with INR's of 1.3 and 1.4.[33] This is in contrast to the European and Scandinavian guidelines, which accept an INR of 1.4 or less as long as the warfarin was stopped for five days.[34,35]

During the discontinuation of warfarin, an LMWH "bridge" therapy may be considered in patients at high risk for venous thromboembolism. However, a study in patients with atrial fibrillation showed that the discontinuation of warfarin without bridge therapy was non-inferior to bridge therapy with dalteparin.[36] This study looked at patients with atrial fibrillation and may not apply to patients with prosthetic cardiac valves.

Heparin and LMWH

Heparin inactivates thrombin (factor IIa) and factors IXa and Xa.[1] Intravenous heparin acts immediately while subcutaneous heparin takes 1 h to work. The therapeutic effect of intravenous heparin ceased at 4–6 h after administration. The half-life of heparin increases with increasing dose: 30 min for the 25 U/kg dose, 60 min half-life of 100 u/kg, and 150 min for the 400 U/kg dose.[37] The anticoagulant effect of heparin was monitored through the activated partial thromboplastin time (aPTT). Therapeutic anticoagulation is achieved when the aPTT is 1.5–2.5 times the initial value. Reversal was achieved with protamine at a dose of 1 mg of protamine per 100U of heparin.

Interventional procedures should be avoided in patients receiving *intravenous* heparin, as these are elective procedures. The patient's pain can be controlled with medications and adjunctive treatment. If a procedure needs to be performed, it should be postponed for at least 6 h after IV heparin is discontinued. The drug is restarted 2 h after the neuraxial injection. If a moderate- or high risk procedure was performed, especially if it was bloody, then a 24 h interval is observed (Table 74.12).

TABLE 74.12 Recommended Intervals Between Stoppage and Resumption of Warfarin, Heparin, and Low Molecular Weight Heparin for Interventional Pain Procedures

Drugs	Drug Discontinuation and Pain Procedure	Resumption of Drug
Warfarin	Five days, INR back to normal	24 h
IV heparin	4 h	2–24 h
BID subcutaneous heparin	6–24 h	2–4 h
TID subcutaneous heparin[a]	6–24 h	2–4 h
LMWH, prophylactic dose	12 h	4–24 h
LMWH, therapeutic dose	24 h	4–24 h
LMWH, dalteparin	24 h	4–24 h
Fibrinolytic agents[a]	48 h	[b]

[a]Interventional pain procedures only when necessary

[b]See text

BID, Twice a day; *INR*, international normalization ratio; *IV*, intravenous; *LMWH*, low molecular weight heparin; *TID*, three times a day.

The ASRA guidelines on regional anesthesia allow the continued use of *BID subcutaneous* heparin, while the pain guidelines recommend that interventional procedures should not be performed until at least 6 h after subcutaneous heparin administration. The drug could be restarted at a minimum of 2 h after the procedure. Regarding *TID subcutaneous* heparin, two studies showed the safety of administering neuraxial injections in patients on subcutaneous TID heparin; 714 and 928 patients were studied.[38,39] These findings led to the recent ASRA guidelines allowing pain injections to be performed 6 h after the subcutaneous heparin but after 24 h in high-risk surgical interventions.[3]

Subcutaneous long-term daily LMWH is the recommended treatment for cancer-associated VTE.[40,41] In patients on LMWH, the ASRA pain (and regional) guidelines recommend a 12 h interval between discontinuation of a prophylactic dose of enoxaparin and interventional pain procedures. For therapeutic doses of enoxaparin (1 mg/kg) and dalteparin, a 24 h interval is recommended. The drug can be resumed 4 h after a low risk pain procedure (Table 74.12).

In cases of moderate or high risk procedures, the resumption of warfarin, heparin, and LMWH should be delayed for 24 h after the procedure (Table 74.12). Drugs that affect hemostasis (antiplatelet, NSAIDs, SSRIs, and other anticoagulants) should not be used concomitantly in patients on these anticoagulants.

Fibrinolytic Agents

Intravascular fibrin clots are dissolved by plasmin, which is derived from the inactive precursor plasminogen. Fibrinolytic agents dissolve fibrin clots. Streptokinase and urokinase dissolve thrombi by activating plasminogen, while alteplase and tenecteplase are more fibrin-selective and have minimal effects on plasminogen. The half-life of fibrinolytic agents is only a few hours, but fibrinogen and plasminogen are decreased for up to 27 h. The ASRA pain guidelines recommend that interventional pain procedures be avoided in these patients. If a pain procedure needs to be performed, a minimum of 48 h should elapse from the time the drug was given to the time the procedure was performed. The 48 h interval is longer than the Scandinavian guidelines, which recommend a 24 h interval between the stoppage of the drug and a neuraxial block.[35] Longer intervals may be preferable given the absence of data on these patients. The time to resume the drug is not known because of the lack of data and the ability of these drugs to dissolve clots. A 24 h interval is reasonable based on the inability of thrombolytic drugs to lyze a cerebral embolic clot after 6 h.[42]

Fondaparinux and the Direct Oral Anticoagulants (DOACs)

CF X is located at the junction of the intrinsic and extrinsic pathways of the coagulation cascade. Fondaparinux is a synthetic factor Xa inhibitor. Direct oral anticoagulants (DOACs) include the factor X inhibitors rivaroxaban, apixaban, and edoxaban. The other DOAC is dabigatran, a direct inhibitor of thrombin, which is the end product of coagulation.

Fondaparinux is a selective CF-Xa inhibitor. Unlike heparin, fondaparinux has a minimal inhibitory effect on thrombin. The drug has complete bioavailability subcutaneously, immediate onset of action, a half-life of 15–20 h, and a direct renal excretion without any metabolism.[43] Fondaparinux is used to prevent

TABLE 74.13 Recommended Intervals Between Stoppage and Resumption of the Direct Oral Anticoagulants and Interventional Pain Procedures, Laboratory Tests, and Reversal

Drug	Drug Discontinuation and Pain Procedure	Resumption of Drug	Laboratory Test	Reversal
Fondaparinux	Four days	24 h		
Dabigatran	Four days (Six days in renal patients)	24 h	Dilute TT ECT	Activated charcoal within 2 h Idarucizumab
Rivaroxaban	Three days	24 h	PT Anti Xa assay	Activated charcoal within 8 h Andexanet alfa
Apixaban	Three days	24 h	Anti Xa assay	Activated charcoal within 3 h Andexanet alfa
Edoxaban	Three days (Six days in renal patients)	24 h	Anti Xa assay	[a]
Betrixaban	Five days	24 h	Anti Xa assay	[a]

[a]Andexanet alfa has not received US Food and Drug Administration approval for the reversal of edoxaban and betrixaban as of July 2020.

ECT, Ecarin clotting time (not readily available); *PT,* prothrombin time; *TT,* thrombin time.

VTE in patients who have had total joint arthroplasty and for the treatment of VTE and PE. Its use is limited in the elderly, patients with low weight, and those with kidney impairment. The ASRA guidelines recommend a five half-life interval or 3–4 day discontinuation before a medium-or high-risk interventional pain procedure is performed (Table 74.13). The drug was resumed 24 h later.

The introduction of DOACs revolutionized the care of patients with VTE and the prevention of stroke in patients with atrial fibrillation. This class of drugs is now recommended by the 2016 American College of Chest Physicians and the 2017 European Society of Cardiology guidelines for deep vein thrombosis and PE.[40,41] The same guidelines suggested DOACs over vitamin K inhibitors or aspirin in the extended treatment of VTE in patients without cancer. DOACs have a wide therapeutic window, require less laboratory monitoring, and are associated with less bleeding than vitamin K antagonists. However, bleeding still occurs, especially in the elderly and inpatients with renal disease.[44] There are no published studies on the safety of DOACs in regional anesthesia and interventional pain procedures, so discontinuation is based on their pharmacokinetics. After five half-lives, 97% of the drug is eliminated compared to 25%, 12.5%, and 1.6% after two, three, and six half-lives, respectively.[18] To ensure that the plasma levels of the anticoagulant are low but not delay the intervention further, the ASRA pain guidelines recommended a five-half-life interval between the last dose and injection.

Dabigatran is approved for the prevention of stroke in patients with non-valvular atrial fibrillation and VTE after knee or hip arthroplasty.[45] Dabigatran is a pro-drug with an onset of 1.5–3 h and a half-life of 14–17 h. It was eliminated by 80% by the kidneys. The presence of renal insufficiency results in the doubling of its half-life, from 14–28 h.[46] Five half-lives, corresponding to four days, is the recommended interval between the stoppage of the drug before performing a pain procedure (Table 74.13). A longer interval of six days should be observed in patients with renal problems. The drug was resumed 24 h after the procedure.

Rivaroxaban is approved for the prevention of stroke in non-valvular atrial fibrillation, prophylaxis, and treatment of VTE, and prevention of VTE after orthopedic surgery in the United States, Europe, and Canada.[45,47] Peak concentrations of rivaroxaban reach 2.5–4 h after intake, and its half-life is 5–13 h.[48,49] Dosing adjustments for rivaroxaban are not required for older patients (>65 years old) with adequate renal function.[50] A five-half-life interval, or three days, is recommended between discontinuation of the drug and medium-and high risk procedures. The drug may be resumed 24 h later (Table 74.13).

Apixaban is a factor Xa inhibitor drug indicated for the prevention of stroke in patients with non-valvular atrial fibrillation and for VTE prophylaxis after hip and knee arthroplasty. Peak plasma concentrations are attained within 3–4 h, and it has a half-life of 8–13 h.[51,52] In patients who are not at high risk for bleeding, three days is recommended between the stoppage of the drug and medium-and high risk interventional pain procedures. The drug was resumed 24 h later.

Edoxaban is a factor Xa inhibitor approved for the prevention of stroke in patients with atrial fibrillation and for the treatment of VTE and PE. The maximum concentration was attained 2 h after intake, and anticoagulation effects were noted within 2 h. The drug is 60% bioavailable, 50% is excreted by the kidneys, and 50% is excreted by the biliary system. Age, sex, and race did not affect the pharmacokinetics of edoxaban. There is a marked reduction in the clearance of edoxaban in patients with severe renal impairment.[53] Its half-life is 10–14 h.[53,54] Five half-lives (55 h or 2.5 days) translates to a three day discontinuation interval before interventional procedures can be safely performed in patients without renal problems. A longer interval (e.g. five–six days) should be considered in patients with renal disease. The drug was resumed 24 h later (see Table 74.13).

Betrixaban is the only CF Xa inhibitor approved by the FDA for thromboprophylaxis in acutely medically ill patients.[55,56] Approval was based on the study that showed betrixaban to be as effective as enoxaparin in preventing VTE in acutely ill patients.[57] The study was supported by two meta-analysis papers that concluded the CF Xa inhibitors, including betrixaban, were associated with a significant decrease in VTE when compared with standard-duration LMWH.[58,59] Betrixaban has 35% bioavailability; the time to reach maximum plasma concentration is 3–4 h, and the half-life is 19–27 h. The primary route of elimination is hepatobiliary (82%–89%); the P-450 system does not play a major role in its metabolism; hence, drug interactions are not a major concern. The recommended dosage is an initial dose of

160 mg orally followed by 80 mg daily for 35–42 days. As with other CF Xa inhibitors, bleeding is a concern. The long half-life is a concern for interventional pain physicians. Five half-lives mean that the drugs should be stopped for five days prior to the pain procedure (Table 74.13).

Laboratory Tests, Reversal, and Management of Direct Oral Anticoagulants Before Emergency Surgery

The mean and trough concentrations of DOACs have been noted, but they are not targeted because their efficacy and safety are not based on specific plasma levels.[49] The activated partial thromboplastin time (aPTT) is prolonged after dabigatran, although the relationship is not linear. There was a greater than linear increase at lower concentrations (at or below 200 ng/mL) and a linear relationship at higher concentrations (>200 ng/mL) (Table 74.13).[60,61] The thrombin time (TT) is highly sensitive to the effects of dabigatran. The ecarin clotting time (ECT) directly measures thrombin generation and is linearly and dose-dependently related to dabigatran concentrations. Prothrombin time (PT) is the least sensitive test, while dilute TT and ECT are the tests of choice for dabigatran.[60]

A linear correlation exists between the effects of rivaroxaban and PT, especially when neoplastin was used as the test reagent (Table 74.13). Compared to rivaroxaban, apixaban had little effect on PT. Edoxaban prolonged PT in a dose-dependent manner, but the assay was not adequately sensitive. There is marked variability in the sensitivity of PT reagents to the CF Xa inhibitors, so every laboratory should calibrate the PT specifically for rivaroxaban, apixaban, and edoxaban to determine the effect of each drug on the test. The anti-FXa chromogenic assay for monitoring direct Xa inhibitors includes analyte-specific calibration. It provides the best choice for monitoring the anticoagulant effect of these drugs.[60]

Activated charcoal prevents the absorption of dabigatran within the intestine, but it needs to be administered within 2 h of dabigatran ingestion (Table 74.13). Idarucizumab is a monoclonal antibody fragment that binds free and thrombin-bound dabigatran. Studies have shown the efficacy of the drug in reversing dabigatran in healthy volunteers,[62] and in patients who had serious bleeding or urgent procedures.[63] The dose of idarucizumab is 5 g intravenously, administered as two 50 mL bolus infusions (2.5 mg), given no more than 15 min apart. The 2019 update of the ACC/AHA/HRS guidelines recommend idarucizumab for the reversal of dabigatran in cases of life-threatening bleeding or urgent procedures.[64]

Activated charcoal must be administered within 8 h of rivaroxaban intake to decrease the absorption of rivaroxaban. Activated charcoal, administered within 3 h of apixaban ingestion, may be effective. Andexanet alfa is a recombinant modified human factor Xa decoy protein that binds and sequesters factor Xa inhibitors. A two-part randomized placebo-controlled study showed andexanet alfa to effectively reduce the anticoagulant effect of rivaroxaban and apixaban.[65] A subsequent trial evaluated the efficacy of andexanet alfa in reversing major bleeding associated with the CF Xa inhibitors (and enoxaparin). After the bolus administration, the median anti-factor Xa activity decreased by 89% from baseline among the patients who received rivaroxaban and by 93% among the patients on apixaban.[66] These levels remained similar during the subsequent 2 h infusion. Andexanet alfa can be administered at a high dose (800 mg IV bolus at a target rate of 30 mg/min) followed by 8 mg/min continuous infusion for 2 h (960 mg) in patients receiving rivaroxaban >10 mg, apixaban >5 mg, or unknown dose, or if given less than 8 h from the last dose of the anticoagulant. Otherwise, a low dose is employed (400 mg IV bolus at a target rate of 30 mg/min) and then a 4 mg/min continuous infusion for 2 h (480 mg).[67] The AHA/ACC/HRS recommends andexanet alfa for the reversal of apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding.[64] Studies on the efficacy of PCCs in reversing DOACs are not conclusive.[68] Its use is counterintuitive since the CF levels in these patients are not diminished.[32]

Anti-depressants

Tricyclic anti-depressants and non-serotonergic anti-depressants were not associated with increased bleeding. Serotonin reuptake inhibitors (SRIs) exert antiplatelet effects. These SRIs reduce the serotonin content of platelets and inhibit serotonin-mediated platelet aggregation.[69-71] Increased bleeding has been noted in patients on SRIs.[72] The antiplatelet effect of SRIs is equivalent to a low dose of ibuprofen. However, patients with pain may be taking other medications that potentiate the antiplatelet effects of SRIs.

Herbal Medications

Garlic affects platelet aggregation, and doses as small as 25 mg/day inhibit platelet aggregation. There is a case report of spontaneous spinal hematoma in an older man who was taking 2000 mg/d of garlic.[73] Garlic, when taken in large amounts, should be stopped for seven days before a painful procedure. Dong Quai potentiated the effect of warfarin, whereas danshen decreased the elimination of warfarin. Therefore the INR should be checked in patients taking these drugs before an interventional procedure is performed. Gingko Biloba inhibits platelet activation factor, and a 36 h discontinuation has been recommended.[3]

New Anticoagulants Targeting CF XI

A new anticoagulant undergoing phase 2 and phase 3 trials targets CF XI of the intrinsic coagulation pathway.[44] Animal studies showed that decreased CF XI and CF XII activities prevent the development of thrombosis, with antibodies to CF XI reducing platelet and fibrin deposition more than CF XII.[74] Patients with an intrinsic deficiency of CF XI have a reduced risk of developing VTE leading investigators to speculate that bleeding from drugs inhibiting CF XI is limited. Two mechanisms of inhibition of CF XI are through the antisense oligonucleotide or monoclonal antibodies.[75] Factor XI antisense oligonucleotide (FXI-ASO) was compared with enoxaparin in preventing VTE after total knee arthroplasty (TKA). FXI-ASO was administered subcutaneously 36 days before surgery, three times for one week during treatment, and four once-weekly doses. In comparison, enoxaparin 40 mg was injected subcutaneously the night before surgery or 6–8 h after surgery and once daily for at least eight days postoperatively.[76] The 200 mg FXI-ASO regimen was noninferior and the 300 mg regimen was superior to enoxaparin. Bleeding was lower with FXI-ASO, and the number of clots was small. The authors considered 0.2 units per mL as the cutoff for CF XI level for effective antithrombotic effect. FXI-ASO has a slow onset of action, making it unsuitable when a rapid anticoagulant effect is desired. A human monoclonal immunoglobulin GI antibody that binds to the active site of CF XIa, preventing it from activating CF XI,

is osocimab. A randomized clinical trial compared osocimab with enoxaparin and apixaban to prevent VTE after TKA. Single intravenous doses of osocimab were compared with 40 mg of subcutaneous enoxaparin or 2.5 mg oral apixaban twice daily for at least ten days.[77] The postoperative 0.6 mg/kg, 1.2 mg/kg, and 1.8 mg/kg doses of osocimab met criteria for noninferiority while the preoperative 1.8 mg/kg met criteria for superiority compared with enoxaparin. The investigators considered doses between 0.6 and 1.2 mg/kg as most promising.[77] Bleeding was observed in 4.7%, 5.9%, and 2% of patients who received osocimab, enoxaparin, and apixaban, respectively.

The mechanism of action of osocimab differs from FXI-ASO: osocimab inhibits CF XI, whereas FXI-ASO blocks the liver synthesis of CF XI. Osocimab rapidly inhibits CF XI: aPTT increases within 2 h of infusion,[78] while it takes several weeks for FXI-ASO to decrease CF XI levels to therapeutic levels.[79] FXI-ASO has a long elimination half-life and suppresses FXI activity by greater than 50% more than one month after the last dose.[75] (there are not enough studies to tighten the tmax and half-lives of the drugs). The long half-life put the interventional pain physician in a quandary about when the drugs should be stopped prior to neuraxial or interventional procedures. The CFXI protein has been endorsed as a possible reversal agent. Both FXI-ASO and osocimab are expensive; hence, cost-benefit analyses must be performed.

COVID-19 Induced Coagulopathy

Infection with SARS-CoV-2, which results in COVID-19, is characterized by coagulopathy and disseminated intravascular coagulation (DIC)-like massive intravascular clot formation. The coagulation is initiated by the activation of monocytes by the virus and damage-associated molecular patterns (DAMPs), release of inflammatory cytokines and chemokines stimulating platelets, neutrophils and lymphocytes. The monocytes express tissue factor initiating coagulation. Additionally, damaged endothelial cells develop procoagulant activity. Laboratory findings include elevations in D-dimer, fibrin/fibrinogen degradation products, and fibrinogen.[80,81] The coagulopathy in COVID-19 is different from classic DIC in that the fibrinogen levels are elevated instead of low, thrombocytopenia is mild and the prothrombin time is only slightly prolonged. These laboratory findings, especially the D-dimer, are markers of critical disease and grave prognosis.[82] Forty percent of patients with COVID-19 have a higher risk of venous thromboembolism (VTE), a ≥4.[83] A rapid systematic review of four studies showed a 25%–53% incidence of VTE.[84]

Thromboprophylactic doses of LMWH, or unfractionated heparin in patients with renal impairment, has been recommended for COVID-19 patients hospitalized unless such treatment is contraindicated; mechanical prophylaxis, such as pneumatic compression devices, is advocated for those with contraindications. This recommendation was echoed by the Italian Society on Thrombosis and Haemostasis[85] and the International Society of Thrombosis and Haemostasis (ISTH).[86] The coagulopathy from COVID-19 can be challenging to control with prophylactic doses of heparin because of low levels of anti-thrombin and high levels of fibrinogen in these patients.[87] Therapeutic anticoagulation has been advised in this scenario and also for patients who deteriorating clinically.[88] This suggestion is based on the findings of fibrin deposition in the lung parenchyma and fibrin-platelet microthrombi in the pulmonary vasculature.[88] Extended thromboprophylaxis after discharge, usually for 35 to 45 days, is proposed for patients with a higher risk of VTE.[85,89] Renal failure is frequent in COVID-19 patients making the heparins (unfractionated heparin, LMWH) the drugs of choice.

The pain medicine physician will not see symptomatic COVID-19 patients but may treat patients who just recovered. Basic coagulation parameters should be determined and the bleeding risk of the procedure stratified before interventional procedures are performed.

Summary and Concluding Statements

The ASRA guidelines on interventional pain procedures stratified the procedures according to the risk of bleeding, allowing the continued use of anticoagulants when the risk is minimal. In contrast to the regional anesthesia guidelines, it is recommended that aspirin and NSAIDs be stopped before medium-and high risk procedures. The two guidelines are mostly similar in their recommendations with respect to warfarin, LMWH, fibrinolytic agents, and fondaparinux. A five-half-life interval between the stoppage of the drug and the interventional pain procedure is recommended for direct oral anticoagulants. Advances in the reversal of DOACs have resulted in better patient care. CF XI inhibitors are currently undergoing clinical trials. Coagulopathy in patients who just recovered from COVID-19 is not known and needs to be studied.

Key Points

Risk of Infection in Interventional Pain Procedures

- SCS infection rates are higher than those of other implantable devices, including cardiac pacemakers and total joint replacements.
- Identification of an SSI is based on physical examination findings of localized pain/tenderness, swelling, erythema, heat, or purulent drainage and cultures, labs, and radiologic findings.
- The most common source of infection is from the patient's own flora.
- Infections involving implantable pain therapies most often require complete explantation for successful treatment.
- Preoperative antibiotics should be administered intravenously (IV) prior to the incision (30–60 min prior to the incision or 120 min of incision for vancomycin).
- Continuation of antibiotics in the postoperative period is not recommended beyond 24 h for clean surgical wounds.
- Appropriate surgical scrubbing of the hands and forearms is a CDC Category IB and NICE recommendation.
- The CDC categories IA and NICE do not recommend routine removal of hair to reduce the risk of SSI, and if hair is removed, clippers are the method of choice.
- The use of chlorhexidine significantly reduces the rate of SSIs and results in cost savings compared to povidone iodine.
- Utilization of decolonization protocols in individuals colonized with MSSA or MRSA reduces the rate of postoperative infections. No data exist to support the use of routine decolonization protocols in patients who were not found to be colonized with *S. aureus*

Anticoagulation Considerations in Interventional Pain Procedures

- Patients with pain are at greater risk for the development of hematoma because they are elderly and may have spinal stenosis; post-laminectomy patients have epidural scarring, decreasing the capacity of the epidural space; larger needles are used in SCS placements; several manipulations of the SCS electrodes are required for optimal placement; and patients may be on SRIs that have antiplatelet effects, in addition to their anticoagulant medications.
- The ASRA guidelines stratified the risk of bleeding according to the type of interventional pain procedure. In low-risk procedures, anticoagulation therapy may be acceptable.
- Aspirin should be stopped for six days if it is being taken for primary prevention (patients with no overt cardiovascular disease) and four days for secondary prophylaxis.
- The duration of NSAID stoppage was based on the five half-lives of the drug.
- For the SCS trial, clopidogrel may be stopped for five days if a test of platelet function, such as the P2Y12 assay, shows adequate platelet activity.

Suggested Readings

Risk of Infection in Interventional Pain Procedures

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PART 7

Pain Management in Special Situations and Special Topics

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Pain Management in Primary Care

KATHERINE E. GALLUZZI

Background and Introduction

Of the myriad problems that present to the primary care clinician, pain is the most common and arguably the most concerning. Since pain can herald something as serious as a heart attack or as routine as an inflamed carbuncle, primary care providers (PCPs) must answer the complaint of pain with alacrity and focused attention. Misdiagnosis can cause an unfavorable outcome for the patient; injudicious or inadequate treatment can undermine trust and devastate a therapeutic relationship.

Basic primary care principles have much to offer in the assessment and treatment of pain. The core values in primary care are compassionate care, embodied by the desire to help through the care of patients and their families; a holistic approach to the person that includes family, culture, and society; continuity of care through the maintenance of an interpersonal bond of trust and respect; reflective mindfulness, which manifests as self-awareness of one's own thoughts and emotions with a sense of presence and attentiveness, and lifelong learning, a practice that requires iterative professional development with the goal of improved patient outcomes. Successful primary care incorporates care coordination, preventive care, access, competence, and appropriate utilization of community-based resources.[1]

PCPs include physicians from the specialties of family, general internal medicine, pediatrics, and emergency medicine; some women also rely upon gynecologists for primary care visits. Recent decades have seen a change in the provision of primary care. The traditional model of a family doctor who knows the patient well and maintains continuity of care has evolved to include independent and collaborative practitioners at the same time that patients increasingly rely upon freestanding urgent care centers and hospital-based emergency departments (EDs). Thus

EDs and urgent care centers function as PCPs for both acute pain presentations and ongoing chronic pain treatment. However, patients seen in these settings are typically advised to follow up with their PCP, making collaboration with other healthcare providers inherent in the delivery of primary care pain management. Members of the primary care pain team include physicians, psychologists, physical therapists, advanced practice providers (nurse practitioners [CRNPs], physician assistants [PAs]), dietitians, exercise physiologists, and others. Specialist consultants for pain management likewise encompass many disciplines, including anesthesiology, neurology, orthopedics, palliative care, psychiatry, physical medicine and rehabilitation, and others.

The concept of a patient-centered medical home (PCMH) arose, in part, as a response to the increasing reliance on multiple healthcare venues and the subsequent potential for fragmentation of care. The Agency for Healthcare Research and Quality (AHRQ) of the United States Department of Health and Human Services[2] characterizes a PCMH as providing comprehensive, coordinated, patient-centered care that is accessible, safe, and of high quality. Establishing primary care clinics or offices as advanced medical homes has been advocated by the American College of Physicians as a care model to provide patient-centered, physician guided care that links patients with a personal physician in the setting of a practice that provides focused, continuity care.[3] This model is ideal for the successful management of pain since peripatetic, episodic contact with multiple health care providers discourages a holistic, coordinated, and inclusive treatment approach.

Patients with chronic persistent pain are some of the most challenging; they are likely to derive the greatest benefit from ongoing, focused care coordinated by a trusted clinician.

Physicians and other staff members within primary care practices have observed that the care of chronic pain patients can be onerous and burdensome, which may reflect a lack of formal education and training regarding pain medicine or inadequate systems for providing such care. Research evidence shows that PCMHs provide higher levels of adherence to treatment guidelines and screening recommendations. Such findings spotlight the need for coordinated patient care systems that provide support for the entire treatment team, including clinicians and staff members.[3,4] Besides the implementation of the PCMH model for pain treatment, an interdisciplinary approach is recommended; with input from appropriate collaborating medical disciplines, a multimodal approach to pain management may include nonpharmacologic, complementary and alternative medicine (CAM) techniques, behavioral therapies, non-opioid pharmacologic treatment, and when indicated and carefully managed, opioid analgesics.

See Chapter 4, interdisciplinary outpatient pain care, for a detailed discussion of collaborative care for persons with pain.

This chapter is concern with the crucial responsibility that PCPs bear in evaluating, diagnosing, and collaborating with other clinicians to treat pain. The focus is upon the primary care approach to common pain conditions. *Using low back pain (LBP) as a model, we will review the biopsychosocial approach to care; patient-provider communication; use of well-validated pain rating scales; and evaluation that includes a physical exam and functional assessment.* The use of provocative maneuvers for determining the cause of pain, the development of a thorough differential diagnosis, and the selection of appropriate diagnostic modalities will also be discussed. Available and well-validated treatments for common pain conditions seen in primary care will be discussed. We will review the use of non-opioid and opioid therapies through the lens of continuity care and emphasize the importance of establishing a therapeutic

relationship based on mutual trust and responsibility. Salient points from the Centers for Disease Control (CDC) guideline for opioid prescribing, which provides PCPs a basis for safe use of opioids in pain management, will be detailed.

Is Pain a Diagnosis or a Symptom?

It is tempting to view "pain" as its own diagnostic entity. There may be instances in which an etiologic injury, lesion, disease process, or other pain generator may not be readily evident (e.g. fibromyalgia). In contrast, some chronic pain states may have disease designations that specify causation, such as postherpetic neuralgia or painful diabetic peripheral neuropathy. ICD 10 includes designated G-codes for "chronic pain, unspecified" and "chronic pain syndrome," which may be construed as useful and consistent with our current understanding of the neuroplastic change that can occur in the peripheral and central nervous systems to generate persistent pain.

However, the initial complaint of pain should always be viewed as a symptom needing careful assessment, not only of its physical manifestation but also its attendant psychosocial effects. Many PCPs hold the privileged position of having had long-term relationships with patients that enable them to assess biopsychosocial contributors to pain that go beyond its immediate physical expression. Experiences of pain have been linked to adverse childhood events (e.g. domestic violence, sexual abuse), which leave permanent yet invisible scars. It has been shown that attention and expectation have been linked to one's experience of pain such that these behavioral traits may worsen or mitigate the intensity of how pain is experienced.[5] The following quote, attributed to Sir William Osler, speaks to this fact: "*It is more important to know what kind of patient has a disease than what kind of disease a patient has.*"

Developing rapport, trust, and understanding allows a full assessment of potential sources of pain (immediate, remote, or ongoing), development of a detailed differential diagnosis, and thorough medical workup that supports or confirms the pain source, which will lead to appropriate next steps in ameliorating or mitigating the patient's experience of pain. Thus pain must be approached as a symptom, with the goal of identifying an accurate diagnosis to facilitate an effective treatment approach. PCPs must also recognize when a consult or referral to a specialist is needed and be ready to collaborate with other healthcare professionals in continuity care for the patient with pain.

Definitions and Types of Pain

In 2020, the International Association for the Study of Pain (IASP)[6] agreed to modify its longstanding definition of pain, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." A fourteen-member international committee voted unanimously to revise this term to: "An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury." The new language, which is supported by evidence-based understanding, highlights that the experience of pain is always subjective and can result from physical injury, tissue damage, or disease states but may also manifest as a reaction to a remote or potential injury. While pain is felt in specific part(s) of the body, there is an underlying and always unpleasant emotional component to the experience of pain, which may stem from psychologic trauma (e.g. adverse childhood experiences, sexual abuse) and/or injury-related experiences earlier in life. The new definition also acknowledges the fact that persons who are unable to verbally express themselves also suffer from pain.[7]

The human experience of pain differs in intensity, quality, and duration as a result of pathophysiologic mechanisms with contributions from an individual's psychological and emotional response. Pain embodies the holistic construct of mind-body-spirit, so a complete understanding of pain requires acknowledgment of the contribution of all three domains. Palliative care teaches that, in addition to physical pain, persons with serious illness and/or those who are facing the end of life experience pain that may encompass psychologic and existential or spiritual pain. Persons who are receiving palliative care that includes psychological support in addition to usual care report better quality of life and greater pain relief.[8]

Pain can be characterized by its timing and duration, type, and location. In terms of timing, pain may be acute (sudden onset), recurrent (relapsing/remitting), or chronic (persistent).

Acute pain is a priority in terms of urgent evaluation, diagnosis, and treatment; it has an abrupt onset that is usually because of a specific cause and has a duration that is limited to three to five months. It represents a large healthcare burden in the United States because of several contributing factors, including about 40 million injury-related visits to EDs and approximately 100 million surgical procedures performed annually.[9] Moreover, 80% of surgical procedures and accidental trauma result in acute pain that affects approximately 100 million individuals. Severe acute postoperative pain may be predictive of persistent postoperative pain, with clinical discomfort that is not referable to other causes (e.g. infection or pain from a preexisting condition) lasting two or more months post-surgery.[9]

Table 75.1 is a partial list of common acute painful conditions that present in primary care.

Episodic, recurrent pain, such as that seen in migraine headache, can represent a unique treatment challenge for the PCP. Because of the unpredictable onset of the headache, some utilize EDs for acute treatment and only infrequently present to their PCP for acute and ongoing treatment.

Most acute pain resolves within a relatively brief timeframe, but it can sometimes persist to evolve into chronic pain. Research evidence has demonstrated that because of neuroplasticity of central

TABLE 75.1 Common Acute Painful Conditions in Primary Care

Acute Pancreatitis	Appendicitis
Arthritis, osteo- and rheumatoid	Bone fracture
Cluster or migraine headache	Endometriosis
Fibromyalgia musculoskeletal Sprain/strain	
Adhesive capsulitis, "frozen shoulder"	Acute gout, gouty arthropathy
Acute myocardial infarction, "heart attack"	Herpes zoster
Renal lithiasis, "kidney stones"	Lacerations, or other injuries
Postsurgical pain	Sciatica
Sickle cell disease/crisis	Herniated nucleus pulposis, "slipped disc"
Stomach or peptic ulcer	Trigeminal neuralgia

nervous system regions involved in pain perception, delayed or inadequate treatment of acute pain can lead to the development of chronic pain.[9–11] Recognition that untreated acute pain may evolve to chronic persistent pain is a mandate for PCPs to address acute pain as timely and effectively as possible.

Over half of patients with chronic pain are managed in primary care practices.[3] Chronic pain is defined as nonmalignant pain persisting beyond the usual time needed for healing that has been present on most days for greater than three to six months.[12,13] According to the National Academy of Medicine (formerly the Institute of Medicine) white paper "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,"[14] the prevalence of chronic pain in the industrialized world is projected to increase as a consequence of an aging population, rising rates of obesity (body mass index greater than 30), improved survival rates for catastrophic injuries such as spinal cord injuries and traumatic limb amputations, increased outpatient surgery with inadequate postoperative pain control, and better public understanding of chronic pain, all of which will increase the use of healthcare resources.

Table 75.2 presents a partial list of common chronic pain syndromes presenting to primary care.

Pain may be further categorized because of type, based on the etiology of the pain, as follows:

Nociceptive pain is caused by an identifiable injury or disease process and may occur after thermal, chemical, or mechanical injury. In response to noxious stimuli, a message is transmitted via the primary afferent nociceptor axon from the periphery to the central nervous system (CNS), e.g. postoperative pain, myocardial or other visceral ischemia, bone fracture or metastasis, sprain or strain.

TABLE 75.2 Common Chronic Pain Conditions in Primary Care

Cancer Pain	Chronic Regional Pain Syndrome
– Type 1 ("causalgia")	
–Type 2 ("reflex sympathetic dystrophy")	
Gynecologic pain Headache	
Dyspareunia-migraine	
Cyclical ovulatory pain -cluster	
Menstrual cramps-tension cephalgia	
Pelvic pain	
Fibromyalgia	**Irritable Bowel Syndrome**
Low back pain	Osteoarthritis
Mechanical-knee	
Sciatica-hip	
Herniated nucleus pulposis -spine	
Degenerative disc disease -hands	
Spinal stenosis	
Post-Operative Pain	**Rheumatoid Arthritis**

Neuropathic pain is defined by IASP as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. It develops as a result of damage to, or dysfunction of, the nervous system." It is caused by damage to the peripheral and central nervous system by disease, injury, drugs, or deficiency, e.g. painful diabetic peripheral neuropathy, phantom limb pain, postherpetic neuralgia, B12 deficiency neuropathy, HIV neuropathy.[10]

Nociplastic pain is pain that occurs without evidence of an identifiable injury or inciting event. This new terminology was developed by IASP to define non-nociceptive/inflammatory, non-neuropathic pain, e.g. irritable bowel syndrome, fibromyalgia.[5]

Patients may experience more than one type of pain at the same time. Examples include the patient with painful diabetic peripheral neuropathy (neuropathic pain) who also has hypertrophic osteoarthropathy of the knee (nociceptive pain); or the patient with shoulder pain that is found to be because of cervical spinal stenosis (neuropathic pain) who also has a longstanding history of fibromyalgia (nociplastic pain).

Pain Assessment

Effective pain management requires accurate assessment and diagnosis, but the first step toward resolving pain is gaining the patient's rapport and trust. Since pain is subjective, clinicians must acknowledge the patient's experience of pain by reassuring them that their complaint is valid and that their pain is real. A useful communication technique involves asking open-ended questions and then allowing the patient adequate time to describe what they are feeling and how it concerns them without interrupting or guiding the conversation. The technique of "ask-tell-ask" [15] used by palliative care clinicians involves "asking" the patient what they feel and believe or understand to be the problem, then repeating to them what was heard with feedback or expanded information from the clinical perspective ("tell"), and then closing the loop by "asking" the patient to repeat what they understood to have been said.

Listening closely to how patients describe their pain can give insight into the type of pain and/or the possible pain generator(s). For example, colicky pain described as "cramping, pressing, crushing, or wrenching" may have a visceral source, while words like "sharp, aching, sore, tender" are indicative of somatic pain. A constant dull ache with an intermittent sharp pain that is provoked by movement suggests musculoskeletal strain or sprain. "Pulsing, throbbing, shooting, stabbing, burning, tingling, electric-shock like, crawling, numb" are descriptions that are characteristic of paresthesia and may indicate that the pain is neuropathic in origin.[16]

During the decade of pain (2001–2010) in America,[17] The Joint Commission mandated that pain be measured as "the fifth vital sign." In response, several well-validated rating scales were developed and implemented, particularly in inpatient settings. Validated questionnaires include the brief pain inventory (BPI),[18] and Wong-Baker faces scale,[19] originally developed for use in children and utilized for nonverbal patients. The utility of these scales has been shown in multiple studies. However, in recent years the focus has shifted from assessment of pain using a numerical or visual scale to an evaluation of the effect of pain upon physical function. A basic assessment of physical function can be performed using the Katz activities of daily living (ADLs) scale, commonly used by geriatricians. The basic ADL functions are dressing, bathing/grooming, feeding, toileting, and ambulating. [20] Eliciting measures of functional status is important since setting goals for analgesia ideally should target specific functional

TABLE 75.3 Pain Scales

Assessing Pain Level	Assessing Impact of Pain on Function	Assessing Multiple Dimensions of Pain
Faces pain scale Numeric rating scale (NRS) Verbal descriptor scale	– Katz basic activities of daily living scale (BADLs) – Functional pain scale – Pain disability index – Roland-Morris disability questionnaire (RDQ)* – Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*	– Brief pain inventory-short form – PEG (pain, enjoyment, general activity) scale – McGill pain questionnaire-short form – Oswestry disability form
Pain Level Assessment in Individuals Unable to Communicate		
Pain Assessment in Advanced Dementia Scale (PAINAD)		
Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC-II)		

*Roland-Morris Disability is used in patients with low back pain, while WOMAC is employed in arthritis.

Sources: Substance Abuse and Mental Health Services Administration (SAMHSA). *Managing chronic pain in adults with or in recovery from substance use disorders*. Rockville, MD: SAMHSA, 2012, pp. 12-4671; Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. *Am Med Dir Assoc*. 2003;4(1):9–15; Meints SM, Mawla I, Napadow V et al. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low back pain. Pain 2018;160(4):833–843. Hadjistavropoulos T, Herr K, Prkachin KM et al. Pain assessment in elderly adults with dementia. *Lancet Neurol*. 2014;13(12):1216–1227; Gloth FM, Scheve AA, Stover CV, et al. et al. The functional pain scale: reliability, validity, and responsiveness in an elderly population. *J Am Med Dir Assoc*. 2001;2(3):110–114.

measures; e.g. does the patient hope to be able to run a marathon or do they simply want to be able to transfer from the bed to the commode without significant pain?

For evaluation of the effect of pain on functional disability, specifically with regard to LBP, the Oswestry LBP disability questionnaire has been well validated.[21] The brief pain inventory-short form (BPI), in addition to directly assessing the severity of pain, also assesses interference of pain with work, sleep, mood, and enjoyment. However, it is not easily used for non-verbal patients or those with cognitive impairment.[18] A differential assessment of dementia, its presenting neuropsychiatric symptoms, and the potential presence of pain is crucial to provide the correct treatment.[22,23]

The inability to verbally communicate does not negate the possibility that a person is experiencing pain. Thus tools required to adequately assess pain may differ depending on a patient's age, condition, and ability to understand. These patients will require the use of alternative assessment tools such as the Wong-Baker faces scale or, in the case of dementia, the pain assessment in advanced dementia (PAINAD) scale.[24] The evaluation and management of patients with dementia are discussed in Chapter 79.

Table 75.3 lists pain assessment tools, and Table 75.4 is a modified version of the PAINAD scale.

TABLE 75.4 Modified PAINAD Scale

Breathing (independent of vocalization)	Normal = 0 Occasionally labored breathing or short periods of hyperventilation +1 Noisy, labored breathing, long periods of hyperventilation, or Cheyne-Stokes respirations +2
Negative vocalization	None = 0 Occasional moan/groan or low level speech with negative quality +1 Repeated trouble calling out, loud moaning/groaning/crying +2
Facial expression	Smiling or inexpressive = 0 Sad/frightened/frown +1 Facial grimacing +2
Body language	Relaxed = 0 Tense, distressed, pacing, fidgeting +1 Rigid, fists clenched, knees pulled up, pulling/pushing away, striking out+2
Ability to console	No need to console = 0 Distracted or reassured by voice/touch +1 Unable to console, distract or reassure +2

Scoring: 0 is no pain, and 10 indicates severe pain

Diagnostic Assessment

Besides the use of a pain scale for rating pain, the following questions are useful in diagnostic assessment:

Is the pain constant, intermittent, or transient?
What relieves the pain?
What worsens the pain?
Where is the pain localized?
Does the pain radiate?

The location of pain is frequently a clue to the origin of the pain. The query "tell me where it hurts" can be modified for patients who can comply to "please point to where the pain is the worst." Visual inspection and manual palpation of the area may yield findings that indicate the source of pain, such as an inflammatory process.

For patients who do not require urgent evaluation, a careful "hands-on" physical exam may provide clues to the painful stimulus. Manual palpation of body regions that are identified by the patient as painful may discover somatic dysfunction(s). Somatic dysfunction is defined in the glossary of osteopathic terminology,[25] as "impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial and myofascial structures, and related vascular, lymphatic and neural elements." Somatic dysfunction is further characterized as acute or chronic; the former is an acutely painful lesion accompanied in early stages by vasodilation, edema, tenderness, and muscle contraction, while chronic somatic dysfunction is an impairment or altered function of inter-related parts of the somatic system, and is characterized by tenderness, itching, fibrosis, paresthesia, and contracture.[26–28]

The mnemonic TART[27–29] is used by osteopathic physicians to guide palpatory examination. TART stands for "tenderness, asymmetry of position, restricted motion, and tissue texture changes." The presence of one or more of these findings points to somatic dysfunction, which may be because of the musculoskeletal lesion itself or secondary to disease or derangement in a body part within the same dermatome. Palpation of a painful body region may also reveal point tenderness or trigger points (focal areas of hyperalgesia) and other subtle clues to the etiology of the pain. Besides trigger points, palpatory findings may reveal altered skin turgor (swelling or bogginess) and/or asymmetry, such as decreased and/or painful range of motion. Asymmetry of the musculoskeletal structures may be because of splinting, favoring, or compensating for the pain generator. Examples of somatic dysfunctions directly associated with musculoskeletal injuries include acute psoas muscle spasm (LBP) or tendon stretch/strain (sprained ankle). Passively moving an affected body part through its normal range of motion may reveal a restriction or physiologic barrier. The term somatic dysfunction has been used as a diagnosis. However, many authors feel that its relevance lies not in naming a diagnosis but rather as a descriptive physical finding.[27,28] Osteopathic manipulative technique (OMT) is directed at restoration of normal anatomic position, range of motion, and function of body structures.

Somatic dysfunction can also occur secondary to neuronal pathways that are "facilitated" or upregulated because of an underlying condition in an organ or viscera. In this case, superficially palpated lesion(s) may signal disease or dysfunction remote from the physical finding, a condition referred to as viscero-somatic reflex.[29,30]

Thus identifying pain's origin solely by its location may be confounded by the phenomenon of referred pain, which is pain felt in one part of the body that is caused by injury or disease of internal structures or organs (e.g. shoulder or upper back pain caused by acute cholecystitis). Viscero-somatic reflexes are representative examples of referred pain. The physiologic mechanism is thought to involve the convergence of multiple sensory neurons on the ascending spinothalamic tract, causing the inability of the brain to distinguish visceral pain signals from more common signals arising from somatic receptors.[30]

Examples of pain that is referred to the back are found in Table 75.5.

Besides localized or referred pain presentations, the location of pain may be diffuse, as seen in fibromyalgia or irritable bowel syndrome. These pain conditions are examples of nociplastic pain, in which the pain location does not specifically point to a diagnostic process.

TABLE 75.5 Examples of Referred Back Pain

Vascular	Genitourinary
Abdominal aortic aneurysm	Endometriosis
Ischemic bowel	Ectopic pregnancy
	Prostatitis
Renal	Gastrointestinal
Pyelonephritis	Cholecystitis
Renal calculi	Pancreatitis
Perinephric abscess	Penetrating ulcers
Infectious	Malignancy
Herpes zoster	Colon cancer
Vertebral abscess	Renal cell carcinoma

See Chapter 37 on chronic widespread pain.

Reassurance that a complaint of pain is valid and warrants concern is the first and ongoing step in the treatment of chronic pain. While complete elimination of the pain may not always be possible, there are several nonpharmacologic and pharmacologic options for the treatment of chronic pain. An optimal outcome relies upon careful selection and trial of appropriate medications coupled with adjunctive therapies such as cognitive behavioral therapy, lifestyle modification, OMT, massage, physical therapy, and others.[31]

Model of Pain in Primary Care: Low Back Pain

Since fundamental principles of low back pain (LBP) management are applicable as an initial approach for many pain presentations in primary care, LBP will serve as an exemplar for diagnosis and management of acute and chronic pain. This approach includes:

- focused triage to determine urgent/emergent status;
- biopsychosocial history and physical examination based upon patient rapport and trust;
- comprehensive, appropriate diagnostic workup;
- selection and application of appropriate therapeutic modalities;
- therapeutic trial(s) with frequent follow up evaluations of efficacy; and
- referrals and consultation(s) as indicated.

A further complete and detailed description of the etiologies and treatment options for LBP is available in Chapter 29.

A review of the major causes of disability in the United States, including spinal cord injury, stroke, limb loss, and other catastrophic events, found that back pain and arthritis are the leading causes of disability.[32] Most people will experience at least one episode of LBP during their lifetime; as noted, most episodes are self-limiting and, with conservative treatment, will resolve within weeks. However, many patients experience recurrence(s) and up to 44% report further episodes within a year; approximately 2% to 7% will go on to develop chronic LBP.[33,34] *PCPs provide the initial evaluation and treatment in 65% of cases and frequently provide the ongoing care as sole providers for patients with LBP.*[35]

LBP can be categorized as acute (immediate onset with less than four weeks' duration), subacute (slow onset with four to 12 weeks' duration), chronic (greater than three months' duration), or recurrent (LBP that reoccurs after a pain-free interval).[34] A summary of LBP diagnostic recommendations in a joint clinical practice guideline from the American College of Physicians and the American Pain Society[36] supports initial triage of patients into one of three broad categories: non-specific LBP; LBP potentially because of spinal stenosis or radiculopathy; or LBP potentially associated with another specific spinal issue for which prompt assessment is necessary or for which there is specific treatment needed. A published review of 15 clinical practice guidelines[37] regarding the initial assessment and diagnosis of LBP in primary care recommends:

diagnostic triage;
history and physical examination to identify red flags;
neurologic testing for radiculopathy;
no routine imaging in the absence of concern for serious pathology; and
assessment of yellow flags based on psychosocial factors.

Diagnostic triage of LBP targets red flag clinical findings that may indicate the presence of systemic illness (e.g. infection, cancer) or imminent neurologic compromise (e.g. spinal cord compression).[35–37] Spinal cord or cauda equina compression are emergencies that are

characterized by rapidly progressive neurologic deficits. Spinal cord compression can be caused by unstable spinal structure, herniation of intervertebral disc(s), trauma, malignant tumor, benign tumor, or infection (e.g. epidural abscess). Patients who present with LBP accompanied by evidence of infection, history of or suspicion for cancer, or rapidly progressive neurologic deficits require urgent neurologic, radiographic, and laboratory evaluation, which are most expeditiously available in a hospital/ED. Pain is usually the first symptom of spinal cord compression. However, motor weakness and sensory findings are present in most patients at diagnosis, and bilateral leg weakness may be elicited in multiple nerve root distributions (L3-S1). Bowel and bladder dysfunction are later findings.[34]

Since early diagnosis and prompt treatment improves outcomes, PCPs must recognize the red flags for cauda equina syndrome that include perineal numbness, difficulty initiating urination or urinary retention, fecal incontinence, or hyporeflexia. Red flags for tumor, infection, or pathologic fracture include age over 50 years, fever, chills, recent urinary tract or skin infection, penetrating wounds near the spine, significant trauma, night pain or pain at rest, steroid or immunosuppressive therapy, substance abuse or intravenous drug use, unexplained weight loss, and progressive motor or sensory deficit.[34–36]

Table 75.6 lists red flag findings for urgent evaluation delineated by potential cause.

Red flags require an immediate evaluation that includes X-rays, computed tomography (CT) scan or magnetic resonance imaging (MRI), laboratory studies, and urgent neurologic assessment. On the other hand, available evidence shows that routine advanced imaging (CT or MRI) is not associated with enhanced patient outcomes in patients who do not present with red flags. Clinical practice guidelines are uniform in their recommendation that imaging or other diagnostic tests in patients with non-specific LBP should NOT be routinely performed. In general, radiographic studies can be delayed for one month, during which time 90% of patients will have reported improvement or resolution of the pain.[38,39]

TABLE 75.6 Red Flag Findings in Low Back Pain

Cancer or Infection	Spinal Fracture	Cauda Equina
Prior cancer or recent infection	History of significant trauma	Acute onset urinary retention
Fever > 100° F	Prolonged use of corticosteroids	Loss of anal sphincter tone
Unexplained weight loss	Age >70 years +/–limited trauma	Saddle anesthesia
Immunosuppression		Global/progressive lower extremity weakness
Intravenous drug use		
Corticosteroid use		
No change or worse with rest		
Age >50 years		
Persistence >1 month		

TABLE 75.7 Yellow Flags for Low Back Pain

Affective depression, anxiety, irritability

Behavioral poor coping skills, sleep disorders, suboptimal adherence to physical therapy/rehab, decreased activities of daily living, multi-substance abuse, social withdrawal

Belief pain is uncontrollable, misinterpretation, somatization. An expectation of technologic cures

Social lack of support, life stressors, punitive social environment, low educational level, history of abuse (e.g. domestic violence, sexual abuse, adverse childhood experiences)

Occupational poor work history, poor job satisfaction or work environment, secondary gain, pending litigation, compensation issues

PCPs should also be able to identify yellow flags that may be predictive of prolonged bouts of LBP and/or poor prognosis. These factors are psychosocial in nature and include affective, behavioral, belief, social, and occupational features.[38] Besides the above, certain pain factors should cause concern, such as the severity of symptoms and impairment of functional capacity. Patients with these characteristics are at risk of developing persistent pain that is difficult to manage with routine care and may develop long term disability. Identification of these risk factors can guide the PCP in making appropriate referrals for psychological and/or social service support. These patients will require an interdisciplinary approach to achieve the best outcome.

Table 75.7 lists yellow flag issues in LBP.

Timing and Description of Low Back Pain

As with any pain complaint, how the patient experiences and describes LBP offers clues to its origin. Clinical communication should validate the complaint and encourage the patient to fully describe the onset and experience of the pain; body diagrams such as that found in the BPI are available in electronic health records, may be used to document the location, dermatomal distribution, and possible referred areas of pain.

PCPs must first establish whether the LBP had an acute versus a slow onset. Sudden, abrupt onset of pain is characteristic of muscle strain/sprain or herniated disc; patients typically are able to pinpoint the activity that caused the pain. Those with disc herniations may describe pain that is worse when sitting. In contrast, LBP with a slow, insidious onset suggests the presence of spondylolisthesis (slippage of one vertebral body on the adjacent one), osteoarthritis, or spinal stenosis. Spinal stenosis pain is aggravated by lumbar extension but improved by sitting or leaning forward (hence, the "handlebar" or "shopping cart" signs).[39]

History/Physical Exam and Provocative Maneuvers

The initial goal of the history and physical examination is to distinguish patients with non-specific (mechanical/musculoskeletal) LBP from those with serious non-spinal or spinal pathology, utilizing red flags as indicators of the latter. For patients without red flag findings, clinicians may proceed by obtaining a holistic medical history (including biopsychosocial factors) and physical examination with a focused neurologic assessment.

The history should include open-ended questions regarding symptom onset, intensity, and location of the pain and its effects on the patient's mobility and function. Specific psychosocial factors to note are the patient's body habitus (frail, overweight, obese) and activity levels, cigarette smoking, alcohol or drug use (especially intravenous drug use), and employment status. Questions regarding the history of psychiatric illness such as depression or anxiety are also appropriate, taking note of any responses that might indicate yellow flag findings.

Observation of the patient's gait and posture can be accomplished by having the patient walk a short distance, turn/pivot, and return. Postural and gait abnormalities and the presence of painful (antalgic) gait should be noted. The patient should then be asked to disrobe adequately to allow a full assessment of the back. This includes a visual assessment of the lumbar lordosis, thoracic kyphosis, and vertebral alignment, noting the presence of scoliosis or other deviations from the normal anatomic structure. Osteopathic assessment includes standing and seated flexion tests to assess for changes in the position of the ilia and ischial tuberosities that may indicate pelvic tilt or sacral un-leveling. Leg length discrepancies should be noted as they may contribute to vertebral strain patterns. Visual inspection and manual palpation may reveal evidence of trophic (neurovascular) change such as hair loss, color or temperature changes, and tissue texture changes (swelling, bogginess, spasm) that give clues to whether the pain is because of specific lesion(s), somatic dysfunction, or from an underlying change in the musculoskeletal/axial structure(s).[28]

Focused neurologic assessment should be part of every evaluation of the complaint of pain. In the case of LBP, muscle strength of the hip flexors, lower extremities, and deep tendon reflexes and presence/absence of the Babinski sign should be assessed. If radiculopathy is suspected, monofilament testing may be useful to locate sensory loss. Clinicians may then utilize several provocative maneuvers to further locate the origin of the pain, including the straight leg raise (SLR), Crossed SLR, and FABER tests. The SLR test is the only sign consistently reported to be sensitive for sciatic nerve involvement secondary to vertebral disc herniation.[40] The test is performed with the patient in a comfortable supine position. The clinician passively elevates the patient's leg to 90 degrees (or to tolerance). If pain that matches the patient's accustomed leg pain occurs at an angle between 30 and 70 degrees, the patient is experiencing radicular pain. The SLR test has shown high sensitivity for detecting the presence of radicular involvement but low specificity for identifying a herniated disc.[41] The Crossed SLR test is done by performing the SLR maneuver on the contralateral leg. If pain occurs, it may indicate a large central lumbar disc herniation.

A related provocative maneuver is the Patrick or FABER test (also called "the sign of four"), which is used to assess hip or sacroiliac problems. FABER is an acronym for *F*lexion, *Ab*duction, and *E*xternal *R*otation. With the patient supine, the knee and hip are flexed to 90 degrees. The foot of the extremity being examined is placed atop the opposite knee. The examiner then slowly abducts the patient's thigh to the physiologic barrier and externally rotates it toward the examining table. The presence of pain or spasm in the groin or limitation of movement is suggestive of hip pathology. There are several tests to confirm sacroiliac joint pain.[29] These are discussed in Chapter 30.

The Schober index is a measure of how well the spine opens, useful for patients in whom spondyloarthropathy is suspected. With the patient in a neutral standing position, the clinician locates and makes a mark at L3 (dimple level). Two more marks, one at 10 cm above and one 5 cm below L3, are made, a total of 15 cm apart. The patient is then instructed to bend forward and touch their toes while the clinician measures between the two marks. Normal spinal motion will result in the two marks being at least 3 cm farther apart in a lumbar-flexed position (e.g. 18/15). A result less than 18/15 indicates that the spine is restricted in range of motion and is indicative of a spondyloarthropathy. This test is similar to the routine osteopathic assessment of musculoskeletal structure in which a standing and seated flexion test is performed.[29]

In the physical exam, objective findings that may supplement the yellow flag evaluation can be assessed through a series of tests named for the orthopedic surgeon who first described them, the Waddell tests for functional back pain.[42] They include the patient's over-reaction during physical examination, superficial or widespread tenderness, a distraction test, lack of an anatomic or dermatomal pattern to the pain complaint, and pain on simulated axial load (top of head pressure). In 1998, Main and Waddell published their concern that these signs had been misinterpreted and misused both clinically and medico-legally and emphasized the importance of viewing back pain within a biopsychosocial context.[43] They state that behavioral signs can develop as a reaction to perceived injury and loss of functional capacity and are therefore not a test of credibility. Thus patients displaying Waddell signs may require both medical management of their pain pathology and psychiatry/psychology consult(s) for the psychosocial and behavioral aspects of their pain.

Waddell scores of three or higher were associated with increased odds of the patient exhibiting somatic over reporting. A recent editorial recommended that the Waddell signs should be utilized as a psychological screener to guide appropriate and continued treatments and befitting referrals.[44]

Description of the Waddell signs can be found in Table 75.8.

TABLE 75.8 Waddell Signs

Superficial tenderness– skin over a wide area of the lumbar region is tender to light touch/ pinch

Nonanatomic tenderness– deep tenderness over a wide area that is not localized to one structure and crosses over nonanatomic boundaries

Axial loading– downward pressure on the top of the head elicits lumbar pain

Acetabular rotation– with the patient standing, lumbar pain is elicited within the first 30 degrees of rotation when the clinician passively externally rotates the patient's shoulder and pelvis together in the same plane

Distracted straight leg raise discrepancy– pain is elicited during a straight leg raise when supine during formal testing, but not on distraction when the clinician extends the knee with the patient in a seated position

Regional sensory disturbance– decreased sensation fitting a stocking-like distribution rather than a dermatomal pattern

Regional weakness weakness, cog-wheeling, or the giving way of many muscle groups that are not explained on a neuroanatomic basis

Overreaction– a disproportionate and exaggerated painful response to a stimulus that is not reproduced when the same provocation is given later. These responses can include verbalization, facial expression, muscle tension, or tremor

Differential Diagnosis and Indications for Consultation

The differential diagnosis of LBP is extensive; a useful schema is to consider causes that are:

mechanical, such as alterations in the bony and/or muscular structures such as herniated discs, spondylolisthesis or non-specific muscle strain/sprain;

non-mechanical (inflammatory, infectious, tumor); or

visceral causes (pain referred from internal organ pathology).[31]

Table 75.9 presents a partial list of diagnostic causes of LBP.

Red flag findings in the setting of acute LBP mandate referrals for an urgent consult and further diagnostic workup. Acute LBP with concern for neurologic compromise requires consultation with orthopedic, neurologic/neurosurgical, and radiologic specialists.[45] If an infectious or inflammatory etiology is suspected, in addition to appropriate laboratory and imaging studies, infectious disease or rheumatology referrals are in order. The vital role of the PCP in differential diagnosis is to swiftly assess the need for and expedite the next-step care of the patient with acute LBP through consultation with other providers; many PCPs will provide aftercare and continuity treatments as indicated.

Inflammatory back disease is typically accompanied by systemic features. The characteristic presentation is of early morning generalized stiffness that improves over the course of the day and with exercise. The onset of pain occurs early in life and presents a lifelong condition. The seronegative spondyloarthropathies include ankylosing spondylitis, psoriatic spondylitis, reactive arthritis, and inflammatory bowel disease.[46]

LBP associated with psoriatic arthritis may be accompanied by dermatologic findings such as plaques, pustular psoriasis, and mouth sores. Gastrointestinal or genitourinary symptoms that precede the onset of LBP may be indicative of reactive arthritis (formerly known as Reiter syndrome). A relatively rare cause of LBP, reactive arthritis can present with extra-skeletal findings such as ocular inflammation, conjunctivitis, and iritis. There may be peripheral joint involvement ("sausage digits") and changes in the sacroiliac joint because of erosion and calcification of anterior longitudinal ligament contributing to the pain. Characteristic X-ray findings of psoriatic arthritis include unilateral sacroiliitis and paramarginal syndesmophytes, findings that differ from ankylosing spondylitis in which sacroiliac involvement is bilateral and paramarginal syndesmocytes are uncommon findings.[47]

Patients with inflammatory disease as the etiology of their LBP should be referred to a rheumatologist for definitive treatment. Conservative treatment may include gentle neck extension exercise and counseling to use caution with the use of neck pillows. Disease modifying anti-rheumatoid drugs, such as the TNF α blockers etanercept, infliximab, and adalimumab, have been shown to decrease vertebral and joint erosion. However, there are currently no longitudinal studies that show they can prevent the need in the long term for surgical vertebral fusion.[46,47]

Infectious causes of LBP, including spinal or epidural abscess and vertebral osteomyelitis, are heralded by fever, rigors, and/or an immunocompromised state. Patients who present with one or more of these findings will generally complain of LBP with localized tenderness. They will be able to point to the painful area on the spine. The infectious source may be a recent spinal injection or epidural catheter, intravenous drug use, trauma, surgery, dialysis, genitourinary, or skin infection. On physical exam, patients will exhibit focal tenderness with palpable muscle spasms and are often unable to bear weight; they may have evidence of needle track marks. Prompt laboratory evaluation will reveal elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein levels, typically associated with mild anemia. Patients with suspicion for an infectious or visceral cause for acute LBP, as previously noted, should be admitted to hospital for a complete workup and immediate medical treatment.[45]

An extremely painful cause of acute LBP is vertebral compression fracture because of severe osteoporosis, which may occur with or without warning or trauma. Patients with severe bone mineral density loss may experience spontaneous compression fractures or occur because of a jarring step or fall. Even in the absence of an established diagnosis of osteoporosis, the presence of a fragility fracture should prompt a thorough workup for causes of metabolic bone disease.

Patients with cancer metastases (breast, prostate, lung, thyroid, or kidney malignancy) may present with pathologic vertebral fractures characterized by extremely high pain levels. A physical exam will reveal marked paravertebral spasm and exquisite point tenderness; the patient may have difficulty with even minor movement or repositioning. Plain film X-rays are adequate to visualize vertebral fractures. However, fractures of the sacrum are not easily seen on standard X-rays or bone scans. If a sacral fracture is suspected, a CT scan or MRI are the radiologic studies of choice. Many vertebral metastases are because of cancer, and more than half of patients with myeloma will present with lytic lesions. Night pain, tenderness to palpation, or percussion of the spinal structures are typical symptoms that should trigger laboratory evaluation that may reveal an elevated ESR, anemia, and serum protein electrophoresis abnormalities indicative of multiple myeloma.[45]

The management of acute lumbar compression or pathologic fracture is directed at allowing the patient to resume normal activity as soon as possible. This may require short term use of immediate-acting opioids for breakthrough or incident (e.g. because of movement or specific treatment) in addition to non-opioid analgesic therapy. Most severe cases will require a surgical consult for vertebroplasty or kyphoplasty. See Chapter 69 for discussion regarding procedures for vertebral compression fractures.

Spinal stenosis is more common with advanced age; it rarely presents prior to age 50. Three age-related processes work together to lead to the spinal cord and nerve root compromise: posterior

TABLE 75.9 Differential Diagnosis of Low Back Pain

Mechanical	Non-Mechanical	Visceral
Lumbar strain/sprain	Neoplasia	Pelvic organs
Degenerative disease Disc	Infection Renal	
Facet joint		
Spondylolisthesis	Inflammatory	Aortic aneurysm
Herniated disc	Osteochondrosis	Gastrointestinal disease
Spinal Stenosis	Paget disease	Fat herniation
Osteoporosis		
Fractures		
Congenital disease		

disc herniation, facet joint changes/spurring, and thickening of the ligamentum flavum. A resultant complaint is of bilateral pain in the buttocks and posterior thighs and ambulation-induced neurogenic pain that localizes to the distal lower leg and calf ("pseudoclaudication"). Physical examination may reveal sensory loss and weakness in the legs, or alternatively, patients may exhibit a completely normal neurologic exam. A diagnostic clue is a report that the pain tends to resolve with sitting or leaning forward.[34] The Kemp test is a simple, provocative physical maneuver in which the examiner passively extends and rotates the patient's spine. If localized pain results indicate vertebral facet disease, pain radiates below the knee usually signals nerve root involvement.

Osteoarthritis (OA), as previously noted, is one of the leading causes of painful disability, and it is increasing in prevalence because of an aging United States population and high rates of obesity. OA is the most common cause of knee and hip pain. Like spinal stenosis, it is an age-related condition. However, genetic factors may influence the development of OA, and obesity may accelerate its onset. OA has three characteristic x-ray findings: osteophyte formation (spurs), joint space narrowing, and marginal sclerosis.[33,44]

Since most acute LBP cases are mechanical/non-specific in origin, most will resolve with conservative treatment. Therefore it follows that most chronic LBP cases are mechanical/non-specific, i.e. caused by persistent and/or recurrent alterations in the musculoskeletal structures. Having ruled out urgent causes or conditions needing emergent or urgent evaluation, consultation, and specific treatment(s), PCPs must next determine whether the patient with non-specific LBP is experiencing radicular symptoms. Since L4-5 and L5-S1 are the most common vertebral levels of disc herniation, L4, L5, and S1 nerve roots may be affected.[44]

Conservative treatment consists of maintenance of mobility and ambulation, avoidance of heavy lifting, progressive exercise as tolerated, and pharmacologic treatment if needed. Multiple studies suggest that most patients with sciatica will recover eventually without surgery. However, for severe, progressive neurologic deficits showing a lack of improvement (six to eight weeks of conservative treatment), radiographic studies and consultation are warranted.[38]

Shared Decision Making

For patients with LBP because of disc herniations who have concomitant high risk medical conditions, PCPs must weigh the risks versus potential benefits of surgery. Essential components of the shared decision making process are to determine the impact of the pain on the patient's quality of life, assess how the patient's physical function is affected (activities of daily living [ADLs]), identify the goals of surgery and potential for full rehabilitation, and determine whether there are other viable nonsurgical alternatives. Such discussions are best undertaken by a trusted PCP but may include the opinions of consultants and other providers in the decision making.

The American Pain Society guideline recommendations[35] for LBP caused by herniated disc disease suggest that there is:

no need for provocative discography to determine if a disc herniation is the source of LBP;

no utility for facet joint or intradiscal corticosteroid injections, or prolotherapy for patients with non-radicular LBP; and

no evidence to guide recommendations for vertebral disc replacement.

The panel further recommends:

discussion of risk versus benefits of epidural steroid injections (including lack of long term benefit);

discussion of risk and benefits of spinal cord stimulation for chronic radicular pain (in light of the high rate of complications following stimulator placement); and

discussion of risks and benefits of surgery for disabling radiculopathy because of herniated lumbar disc.

Recent studies showed that nonsurgical interventional interventions compare favorably with surgery. A four-year follow up study of 124 patients with symptomatic lumbar disc degeneration of greater than one year's duration compared the outcomes of surgical versus nonsurgical therapy. One group underwent surgical lumbar fusion while the others were given a cognitive intervention and exercise therapy. The subjects were analyzed for physical function, global disability, work, medication use, emotional distress, and quality of life measures. The outcome analysis showed that 24% of the cognitive intervention and exercise group ultimately underwent surgery, and 23% of the surgical group underwent a second surgery. There were no differences in return to work, pain, disability index, or emotional distress between the two groups. The researchers concluded that long term improvement was no better in the surgical group compared with nonsurgical management consisting of cognitive intervention and exercise.[48]

The spine patient outcomes research trial (SPORT) was a large multicenter study involving 13 centers in 11 states in the United States.[49,50] Patients with chronic LBP because of intervertebral disc herniation, spinal stenosis, and degenerative spondylolisthesis (slippage of the vertebral segment on the adjacent one) were followed for nine years. One group underwent standard open discectomy while the comparison group received nonoperative treatment individualized to the patient. It was found that both groups continued to improve with time (i.e. over the course of six to 12 months). The researchers concluded that for chronic LBP, surgical versus nonsurgical outcome results are equal. In contrast, surgery may be superior for patients with radicular symptoms with respect to improvement in pain, function, and disability throughout the ensuing two and four years postoperatively. However, no significant treatment benefit of surgery was found for chronic LBP from intervertebral disc herniation, spinal stenosis, degenerative spondylolisthesis in six to eight years of long term follow up. Both groups (surgery versus nonsurgical treatment) tended to improve with time.

Management of Chronic Low Back Pain

Most cases of LBP because of musculoskeletal strain/sprain and many because of vertebral disc herniation or degenerative disc disease will resolve with conservative therapy. Unfortunately, a high rate of recurrence and development of chronic LBP are also common, necessitating the expertise of PCPs for providing long term pain management.

Several expert panels have developed clinical practice guidelines for the approach to diagnosis and management of LBP, including the American College of Physicians (ACP) and the American Pain Society (APS), who have published joint recommendations.[36–38,51,52] The North American Spine Society's evidence based clinical guideline for the diagnosis and treatment of LBP recently completed an exhaustive guideline summary review of evidence based recommendations for diagnosing and treating adult patients with non-specific LBP. An interdisciplinary panel of pain experts developed 82 clinical questions, for which the

answers are summarized in their publication. The authors state that the statements reflect the literature as of February 2016."[53]

The following is a brief summary of the recommendations and levels of evidence for treatment of chronic LBP (CLBP) by the clinical guidelines committee of the ACP.[51]

1. The initial approach to chronic CLB should focus on:
   - nonpharmacologic treatment, including exercise, multidisciplinary rehab, acupuncture, mindfulness-based stress reduction (moderate evidence);
   - tai chi, yoga, motor control exercise, progressive relaxation, EMG biofeedback, low level laser therapy, operant therapy, cognitive behavior therapy, or spinal manipulation (low quality evidence).
2. If there is an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment:
   - nonsteroidal anti-inflammatory drugs (NSAIDs) as first line or tramadol or duloxetine as second line;
   - opioids only if failed other treatments and only if the benefits outweigh the risks (weak recommendation).
3. The ACP clinical guidelines committee has rated the evidence for nonpharmacologic treatment of CLBP[51] and concluded that:
   - superficial heat moderately improved pain relief (at five days) and disability (at four days) and, combined with exercise, improved Roland disability questionnaire (RDQ) scores at seven days, with better outcomes than acetaminophen/ibuprofen treatment;
   - acupuncture was found to have conflicting evidence for efficacy but did show a moderate improvement in pain intensity;
   - massage therapy gave some relief to some patients and is considered safe;
   - spinal manipulation therapy improved pain and function if used for four weeks or less, but there was no long term benefit observed;
   - exercise, including stretching, strengthening, or flexion/extension, are not recommended by either the United States or European guidelines. However, exercise is known to confer other benefits;
   - optimal time to start exercise after the onset of LBP symptoms is unclear; for patients in the subacute phase (less than four to eight weeks), rehabilitation (physician, physical therapy, psychological or vocational interventions) are moderately effective (yoga and tai chi have had some promising outcomes for CLBP).

The role of psychiatric and/or psychologic therapy is integral as part of self-management techniques for chronic pain in general, and this applies equally to patients with CLBP.[54] PCPs should be familiar with the resources available for psychiatric and psychologic support and comfortable with making referrals for patients with chronic pain. Good evidence supports the effectiveness of cognitive behavior therapy (CBT), a psychological approach that identifies problematic thought or behavior patterns and works to modify them through active change. A related psychotherapeutic option is acceptance commitment therapy (ACT), which assists the patient in coping with a diagnosis through the steps of acceptance and commitment to improved outcome. These therapies are useful adjuncts to a comprehensive pain approach since they assist patients in setting appropriate goals, recognizing personal barriers, and promoting self-management and self-efficacy. A comprehensive review of nonpharmacologic CAM therapies for pain management is found in Chapter 61.

The following discussion will examine some of the recent evidence for massage, manipulation, acupuncture, exercise, and structured practices such as yoga and tai chi. Massage therapy is considered safe and potentially beneficial for patients with subacute and chronic non-specific LBP, especially when combined with exercise and self-management education. However, two systematic reviews yielded insufficient evidence to make definitive recommendations.[55,56] The authors did note that moderate evidence suggests that combination therapy (massage plus another active treatment such as acupuncture) improved pain and function better than monotherapy alone. Further, as previously noted, spinal manipulation showed improved function for patients with LBP of less than four weeks' duration, but there was no evidence for long term benefits. With respect to acupuncture, data is limited and conflicting. Cherkin et al.[57] reviewed the evidence for safety and effectiveness of acupuncture, massage, and spinal manipulation and concluded that some initial studies have found massage to be effective for CLBP and that the benefits of spinal manipulation are equivalent to those of other therapies; the cost effectiveness of massage, but not for manipulation or acupuncture, may reduce costs after an initial course of therapy.

It seems counterintuitive, but neither the United States nor European guidelines recommend exercise (stretching, flexion, extension, or strengthening) because of a lack of evidence to support its use. Two clinical practice reviews[58,59] do support exercise as important in the maintenance of physical function and note that for patients in the subacute phase of LBP (less than four to eight weeks of pain), rehabilitation that includes the primary care physician, physical therapy, and psychological and/or vocational interventions is moderately effective. "The bottom line is that any physical therapy approach that encourages and enables the individual with acute LBP to resume his or her normal activities is the one to be recommended."[58]

A recent study of 479 patients with chronic LBP compared yoga and physical therapy stretching and strengthening and found outcomes that were similar in acute pain outcomes. Yoga and PT were also found to be similar for secondary outcomes such as pain medication use, global improvement, satisfaction with the intervention, and health related quality of life. In brief, they found that a manualized yoga program for non-specific CLBP was noninferior to PT for improvement in function and pain.[60]

In general, the current evidence is insufficient to determine the effectiveness of transcutaneous electrical nerve stimulation (TENS), electrical muscle stimulation, short-wave diathermy, traction, cold, lumbar supports, motor control exercise, psychological therapies (CBT, imagery relaxation, cognitive coping), Pilates, ultrasound, or taping for CLBP.[35] However, many patients dissatisfied with conventional medical treatment do seek and employ CAM therapies and anecdotally report good effects. Thus PCPs should be knowledgeable about these options and maintain an open mind regarding the utility of nonpharmacologic and/or CAM therapies as part of a multimodal approach to CLBP.

Pharmacologic Therapy for Low Back Pain

The goal in prescribing medications for acute non-specific LBP is not curative; instead, medications may be indicated to reduce symptoms of pain and spasm, which can cause positional discomfort or splinting and consequent reduced movement/mobility as well as difficulty sleeping. The treatment goal is to enable the patient to remain as physically active as possible during the acutely painful period, allowing a transition to healing, hopefully with complete resolution of the pain.

PCPs should determine whether medication(s) will be needed for a brief time (acute/subacute LBP or recurrence) or as ongoing therapy for CLBP. Many medications that are helpful in the short term (acetaminophen, smooth muscle relaxants [e.g. cyclobenzaprine], NSAIDs [e.g. diclofenac, ibuprofen, naproxen sodium], opioids [e.g. codeine, oxycodone]) have contraindications and limitations for long term use. Good evidence exists for the effectiveness of NSAIDs. In terms of analgesia, there is no significant difference between cyclooxygenase inhibitors (cyclo-oxygenase [COX] 2-selective) or traditional NSAIDs. However, their use is limited by the class effect on renal function, gastrointestinal mucosal erosion, and importantly, the black box warning against thromboembolic cardiovascular events, as noted in the subsequent section on general precautions for non-opioid pharmacologic therapy.

The 2007 ACP clinical guideline that reviewed noninvasive treatments for acute, subacute, and chronic LBP[36] was updated in 2017 by a systematic review of systemic therapies for LBP.[49] The following summarizes the 2017 ACP clinical practice guideline:

Acetaminophen (APAP): appears to be no different from a placebo for acute or subacute LBP regarding pain intensity or function through four weeks; no indication for chronic LBP (moderate quality evidence); NSAIDs showed no difference than acetaminophen at three weeks or less; although estimates favored NSAIDs for pain relief, acetaminophen had a lower risk for side effects.

NSAIDs: were associated with greater mean improvements in pain intensity than placebo for acute back pain; for chronic LBP, NSAIDs were associated with greater mean pain relief than placebo after 12 weeks; no clear differences between NSAIDs for acute or chronic LBP; for radiculopathy, small and inconsistent effects were found. NSAIDs were associated with more adverse effects than placebo, but COX-2 inhibitors had a lower risk for adverse events (AEs).

Opioids, tramadol, and tapentadol: no difference for acute LBP between oxycodone or acetaminophen plus naproxen or placebo plus naproxen; for chronic LBP, strong opioids were associated with greater short term relief than placebo; tramadol also resulted in greater short term relief than placebo. Opioids had a higher risk for nausea, dizziness, constipation, vomiting, somnolence, and dry mouth than placebo.

Skeletal muscle relaxants: superior to placebo for short term pain relief; evidence insufficient to determine effects on function or for CLBP; no significant differences among various skeletal muscle relaxants on any outcome.

Benzodiazepines: no clinically significant benefit compared with placebo were associated with CNS AEs (somnolence, fatigue, and lightheadedness).

Anti-depressants: no difference in pain between tricyclic anti-depressants or selective serotonin reuptake inhibitors for CLBP; can be effective, but their mechanisms of action are not clearly understood; serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine was associated with lower pain intensity at 12 to 13 weeks, although effects were small; duloxetine associated with greater improvement in function on the BPI.

Anti-convulsant medications: gabapentin provides small short term benefits for radiculopathy; evidence insufficient to determine effects of pregabalin versus other medication or pregabalin plus another medication versus the other medication alone.

Systemic corticosteroids: no differences were found for non-radicular and radicular LBP compared with placebo when given parenterally (single injection) or a short oral taper; serious harms were not reported.

Consensus panels[36,49] agree that opioid therapy is not useful for the long term treatment of CLBP. Short term, low dose opioids may be needed for patients with traumatic back injuries or fractures, but their use should reflect best clinical practice recommendations, such as the 2016 CDC guideline for prescribing opioids for chronic pain (a guideline review follows).

General Precautions for Non-opioid Pharmacologic Therapy

When considering the use of pharmacologic agents for treatment, providers should be familiar with the mechanism(s) of action (MOA), routes of administration, dosages, pharmacokinetics, side effects, drug interactions, and risks for AEs. These details are presented to supplement the pharmacologic choices outlined by the ACP[49] noted above.

Acetaminophen (APAP)'s analgesic effect may include metabolism to a prodrug that acts partly as a cannabinoid because of the indirect activation of cannabinoid CB-1 receptors. A dual MOA may result in both direct analgesic and modulation effects.[61,62] While considered a first line option, acetaminophen is a slightly weaker analgesic than NSAIDs (equivalent to ten points on a 100 point visual analog pain scale). The main adverse event associated with acetaminophen is hepatotoxicity.[36,38]

Concomitant administration of drugs that induce or regulate CYP2E1 may alter APAP metabolism and increase hepatotoxic potential. Chronic high dose APAP can increase the international normalized ratio in some anticoagulated patients.[63]

The mechanism of action of NSAIDs is inhibition of COX, which is the enzyme responsible for the biosynthesis of prostaglandins and thromboxane. Nonselective NSAIDs inhibit both COX-1 and COX-2, while COX-2 selective NSAIDs only inhibit COX-2. The APS-ACP review[38] showed that NSAIDs were associated with small to moderate pain improvement compared with placebo (moderate quality evidence) and no to a small improvement in function (low quality evidence). Most head-to-head trials of one NSAID versus another showed no differences in pain relief in patients with chronic LBP. Nevertheless, NSAIDs were positioned as first line therapy; there were no data regarding COX-2-selective NSAIDs.

An important contraindication that applies to the entire class of NSAIDs is the risk of thromboembolic cardiac and cerebrovascular events; there is a Food and Drug Administration (FDA) warning of risk for heart attack and stroke as early as the first weeks of use. Thus NSAIDs must be avoided in individuals with known coronary artery disease (CAD), angina, or history of stroke and those at greater than average risk for these conditions. It is further recommended that NSAIDs be avoided in individuals with kidney disease, congestive heart failure (CHF), or cirrhosis. They are not recommended in the third trimester of pregnancy.

AEs associated with NSAIDs include gastrointestinal (GI) toxicity, although the COX-2 selective NSAID (celecoxib) has less potential to cause ulcers or GI bleeding, liver and kidney toxicity, hypertension, and CHF. In terms of drug interactions, NSAIDs must be used with caution in patients on diuretics. They also pose a significantly increased risk of bleeding in patients on low dose acetylsalicylic acid or taking any anticoagulant. They should not be co-prescribed with phenytoin or cyclosporine. NSAIDs are available in oral, topical, IV formulations.[64,65]

TABLE 75.10 NSAID Dosages

Drug	Starting Dose	Maximum Dose
Celecoxib	100 mg PO BID	200 mg PO BID
Diclofenac DR	50–75 mg PO BID	150 mg/day
Diclofenac ER	100 mg PO QD	100 mg PO QD
Ibuprofen	200–400 mg PO TID–QID	2400 mg/day
Meloxicam	7.5 mg PO QD	15 mg/day
Naproxen*	250–500 mg PO BID	1000 mg/day

*Naproxen 250, 500 mg = naproxen sodium 275, 550 mg.

Table 75.10 lists starting and maximum dosages for NSAIDs.

Tricyclic anti-depressants (TCAs) have an MOA that involves inhibition of the reuptake of both serotonin and norepinephrine. Although well studied in various pain conditions and despite their use for many decades as first line treatment for neuropathic pain, none of the tricyclics carry an FDA indication for pain management. The doses used for pain must be slowly up-titrated over several weeks (e.g. 10 mg/day to a maximum dose of 100 mg/day). TCAs are absolutely contraindicated for use in patients taking monoamine oxidase inhibitor (MAOI)s, and they should be avoided in patients with severe cardiac disease (pretreatment electrocardiogram [ECG] is recommended because of effects on the QTc interval) and in patients with severe GI dysfunction. The FDA lists a class effect black box warning for suicidal thinking and behavior in children, adolescents, and young adults. Because of their strong serotonergic effect and metabolism with CYP3A4 and CYP2D6 substrate, TCAs may lower the seizure threshold or cause hyponatremia.[66] The AEs that are associated with TCAs are generally anticholinergic: blurred vision, cognitive changes, constipation, dry mouth, orthostatic hypotension, sedation, sexual dysfunction, tachycardia, and urinary retention.[67–69]

SNRIs are a class of anti-depressants that cause inhibition of the reuptake of two neurotransmitters: serotonin and norepinephrine. They have indications and uses for pain management as well as for depression. APS-ACP review[36] (moderate quality evidence) showed no difference in pain between tricyclic anti-depressants (TCAs) or selective serotonin reuptake inhibitors versus placebo and showed no differences in function for anti-depressants (low quality evidence). However, moderate quality evidence showed that duloxetine was associated with a small improvement in pain intensity and function compared with placebo, so it is recommended as second line therapy.

Duloxetine has indications for chronic musculoskeletal pain such as LBP and OA, fibromyalgia, and painful diabetic peripheral neuropathy; milnacipran is indicated for fibromyalgia. Venlafaxine, which is indicated for depression and anxiety, may be effective in acute and chronic neuropathic pain and painful diabetic peripheral neuropathy (PDPN). Usual starting doses for duloxetine are 30 mg/day for chronic musculoskeletal pain and fibromyalgia and 60 mg/day for PDPN with a maximum dose of 120 mg/day. SNRIs are contraindicated for use with monoamine oxidase inhibitors (MAOIs).

TCAs carry a black box warning for suicidal thinking and behavior in children, adolescents, and young adults. Since SNRIs are potent inhibitors of CYP1A2 and 2D6, it is recommended to monitor liver function during use.[38,66]

The MOA of anti-convulsants is dependent upon the specific drug. The gabapentinoids (pregabalin and gabapentin) and valproic acid act through voltage-gated calcium channel modulation while carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid act via voltage-gated sodium channel modulation. Carbamazepine, oxcarbazepine, lamotrigine, gabapentin cause inhibition of glutamate release, while valproic acid topiramate increases GABA inhibition.

Anti-convulsants have several indications and use for pain management. Gabapentin is indicated for postherpetic neuralgia and may be effective in painful diabetic neuropathy. Pregabalin is indicated for painful diabetic neuropathy, postherpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal cord injury.

Carbamazepine has an indication for trigeminal neuralgia. Other anti-convulsants have been studied in pain conditions and may be considered as the second line if other options have failed.

Coadministration of gabapentinoids and opioids increases the risk of respiratory depression. Commonly reported side effects (incidence greater than 5% and more than twice the rate observed with placebo) are dizziness, somnolence, and peripheral edema.[67]

Regarding the efficacy of anti-convulsants in LBP, evidence was insufficient to determine the effect of anti-convulsant medications on acute, subacute, or chronic low back pain, nor was there sufficient evidence to determine the effect of anti-convulsant medications on radicular low back pain.[38]

Table 75.11 lists typical dosages for anti-convulsants.

TABLE 75.11 Anti-convulsant Dosages

Drug	Starting Dose	Target Dose	Side Effects	Renal Exc	Hepatic Pathways
Gabapentin	100–300 mg	3600 mg	Weight gain, dizziness, sedation, ataxia, diplopia, twitching, HA*	>95%	No
Pregabalin	25–50 mg	900 mg	Weight gain, dizziness, sedation, ataxia, diplopia twitching, HA*	>95%	No
Oxcarbazepine	300 mg	2400 mg	Hypo Na^{++}, SJS, ** and EM***	30%	Yes, ~50%

*headache.
**Stevens-Johnson Syndrome.
***erythema migraine.

Summary of Treatment Recommendations for Low Back Pain

The choice of medication for LBP should be evidence based and tailored as much as possible to suit the individual patient. Acetaminophen, mild opioids, and NSAIDs are the first line drugs for LBP, but there is no evidence that one is more effective than the others. Nonbenzodiazepine muscle relaxants (with or without pain medication) could be considered second line drugs in acute LBP and cyclic antidepressants in chronic LBP. The risk of adverse side effects can be reduced by taking into account the patient's medical history and using a test dose. The realization that symptoms other than pain are sometimes more important and/or easier to overcome can increase the benefits of medication. The long term effects of medication can be improved when combined with non-drug interventions.[70]

Recognizing that most patients with acute and subacute LBP without red flag findings will improve over time regardless of treatment, PCPs may decline to order costly tests and potentially harmful treatments. Genuine acknowledgment of the patient's complaint of pain within the context of a trusted patient-provider relationship is a springboard to focus patient education on the benefits of nonpharmacologic treatment options and lifestyle adaptations such as weight loss, maintenance of physical activity, and progressive exercise. Since few differences in recommended therapies were found in comparison trials, treatment recommendations should be based on patient preferences, cost, and harm avoidance. Preserved function is the important goal that should supersede attempts at complete resolution of pain.

As noted by the American Board of Internal Medicine's choosing wisely guidelines,[71] initial nonpharmacologic treatment for LBP may include superficial heat, spinal manipulation (e.g. osteopathic manipulation or chiropractic treatment), massage, or acupuncture. Patients should be advised to remain as active as tolerated, and prolonged bed rest should be discouraged. However, PCPs may prescribe modifications to work duties such as avoidance of heavy lifting, bending, twisting, and/or prolonged sitting. Multimodal therapy, or a combination of treatments, may provide additional benefit (e.g. heat coupled with massage and other nonpharmacologic treatment).

If pharmacologic treatment is needed, topical analgesics, acetaminophen, NSAIDs, or skeletal muscle relaxants may be considered. However, steroids have shown no appreciable effect, even in radicular LBP. For patients with CLBP and inadequate response to nonpharmacologic therapy, consider pharmacologic therapy with NSAIDs first with tramadol or duloxetine as second line therapy. Opioids should be considered only for patients with moderate to severe pain who have failed to adequately respond to non-opioid and nonpharmacologic treatments and for whom the potential benefits outweigh risks.[72,73] A comparison of long term opioid versus non-opioid pain management therapy for patients with LBP, hip, or knee osteoarthritis showed that the two treatment groups had similar levels of pain reduction. However, opioids have many associated side effects and significant risks.[74]

If opioid therapy is contemplated, shared decision making and use of a patient-provider agreement or therapeutic contract that delineates the roles and responsibilities of each is recommended. A discussion of opioid use in primary care with an emphasis on the FDA blueprint and CDC guideline follows. Finally, with respect to the management of LBP, basic knowledge of the available interventional procedures is useful so that PCPs can make appropriate referrals, educate patients regarding potential risks and benefits, and provide aftercare and ongoing management as needed. A discussion of interventional procedures for LBP is beyond the scope of this discussion. However, detailed information about interventional pain management can be found in part IV: neural block and interventional techniques of this text.

Table 75.12 lists interventional procedures for LBP.

TABLE 75.12 Interventional Procedures for Low Back Pain

Epidural steroid injections Spinal drug delivery
Steroid intraarticular injections Discography
Spinal cord stimulation for LBP and neuropathic pain Botulinum toxin
Intrathecal therapy for LBP Trigger point injections
Sacroiliac joint injection and RFA
Facet joint injection and RFA
IDET, nucleoplasty, disc RFA

IDET, Intradiscal electrothermal therapy; *LBP*, low back pain; *RFA*, radiofrequency ablation.

Musculoskeletal Pain in Adults

Many pain complaints (e.g. strains, sprains, bursitis, tendonitis, arthritis) that present to the PCP have their origin in the musculoskeletal system. The Global Burden of Disease Study showed that musculoskeletal injuries of the neck, shoulder, knee, and other body parts cause diminished quality of life, disability, and increased healthcare costs.[75] A systematic search (including Cochrane Reviews) of potential therapies for musculoskeletal pain was conducted by the Arthritis Research United Kingdom Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keela University, Keela, United Kingdom.[76] Moderate evidence showed that exercise therapy and psychosocial interventions are effective for relieving pain of musculoskeletal origin. While NSAIDs and opioids reduced pain in the short term, the effect size was modest, and the risk for adverse effects signals need for consideration. For knee and shoulder pain, corticosteroids were found to provide short term pain relief. However, based on the evidence, the findings were equivocal regarding dose, intensity, frequency, or mode of application for these therapies.

Four out of five injuries treated in physician's offices are musculoskeletal, with an estimated cost of $176.1 billion in 2010.[77] A joint guideline published by the ACP and American Academy of Family Physicians (AAFP)[78] gave recommendations regarding management of acute pain from non-low back musculoskeletal injuries in adults considered the following treatment parameters: pain relief at one to seven days, physical function, treatment satisfaction, symptom relief, AEs (dermatologic, GI, and neurologic) and comparative harms of nonpharmacologic and pharmacologic treatments. The review also considered patient values and preferences, costs, areas of inconclusive evidence, and clinical considerations for patients with multiple chronic conditions. The guideline's expert panel noted that those with more chronic conditions have a higher probability of receiving opioids for prolonged periods. The ACP/AAFP guideline:

1. Recommends that clinicians treat patients with acute pain from non-low back, musculoskeletal injuries with topical NSAIDs with or without menthol gel as first line therapy to reduce or relieve symptoms, including pain; improve physical function; and improve the patient's treatment satisfaction.

2. Suggests that clinicians treat patients with acute pain from non-low back, musculoskeletal injuries with oral NSAIDs to reduce or relieve symptoms, including pain, and to improve physical function, or with oral acetaminophen to reduce pain; and suggests that clinicians treat patients with acute pain from non-low back, musculoskeletal injuries with specific acupressure to reduce pain and improve physical function, or with TENS to reduce pain.
3. Suggests against clinicians treating patients with acute pain from non-low back, musculoskeletal injuries with opioids, including tramadol.[78]

The ACP/AAFP guideline rationale notes that topical NSAIDs improved all outcomes compared with placebo and were not associated with increased risk for harm. Few harms were reported except for oral NSAIDs, which caused GI AEs: it emphasized that clinicians must assess GI risk factors prior to prescribing oral NSAIDs. The rationale for recommendation[3] notes that treatment with opioids was associated with significant increases in risk for neurologic and GI AEs and cites evidence that showed a relationship between prescriptions lasting longer than seven days. It was again noted that prolonged use of opioids carries the risk for long term addiction and overdose.

Multimodal Therapy and Nonpharmacologic Options for Managing Pain

The choice of medication, dose, route, and duration of therapy should be individualized to implement multimodal therapy (i.e. synchronous administration of two or more pharmacologic agents or approaches, each with a distinct mechanism of action). The rationale for multimodal therapy is that different modalities target different receptors and pain pathways such that multiple agents provide a synergistic or enhanced effect. This technique allows for dose reduction of individual agents, which may lead to less risk of an individual drug's adverse effects, assuming, of course, that there are no adverse drug-drug interactions.

While the evidence for some nonpharmacologic modalities is mixed and/or limited, they nonetheless serve as a complementary approach for pain management and, in some circumstances, may reduce the need for opioid medications. PCPs may promote nonpharmacologic therapies by ensuring that patient preferences are discussed and by identifying community resources that provide complementary therapies relevant to their patient population. Nonpharmacologic strategies include but are not limited to physical modalities (acupuncture, aqua therapy, chiropractic therapy, osteopathic manipulative treatment, massage therapy, and physical therapy); movement therapy (dance, tai chi, yoga); psychological (behavioral modification, cognitive restructuring, CBT, ACT, psychiatric therapy); and relaxation therapy (mindfulness, meditation). Other CAM modalities include balneotherapy (heat), aromatherapy, and music therapy.

Table 75.13 lists alternative nonpharmacologic and non-opioid pharmacologic treatments.

TABLE 75.13 Alternative Treatments for Pain

Nonpharmacologic Therapies	Non-opioid Pharmacologic Therapies
Psychological approaches Cognitive behavioral therapy (CBT)	NSAIDs and acetaminophen
Physical rehabilitative approaches Physical therapy Occupational therapy	Anti-convulsants
Surgical approaches	Anti-depressants
Complementary therapies Acupuncture Chiropractic	Local anesthetics Topical Blocks
Osteopathic manipulative medicine	Other adjuvant medications

Source: Food and Drug Administration. *FDA education blueprint for health care providers involved in the management or support of patients with pain. Draft revisions.* Available at: https://www.fda.gov/downloads/Drugs/NewsEvents/UCM557071.pdf.

Pharmacologic Approach to Pain and Opioid Use

The "decade of the brain" (1991–2000) in the United States resulted in many advances in neurosciences. It was followed by "the decade of pain control and research" (2001–2010) through the passage of House of Representatives bill, H.R. 3244, which President Clinton signed into law. The goal of this program was to bring "a much needed focus on pain disorders, to benefit both the public and private sectors by stimulating further advances in research, education and clinical management of pain disorder."[17] This enhanced interest in assessing and treating pain may have led to the joint commission recommendation that every patient's level of pain be regularly measured as the "fifth vital sign." Within this setting, pharmaceutical manufacturers developed and brought to market several new, potent, extended-release, long-acting opioid formulations, most of which were heavily marketed. The subsequent decades saw a significant increase in the use of opioid analgesics.

In response to increased opioid use and the observed rise in prescription opioid overdose deaths in the United States, the FDA imposed a risk evaluation mitigation strategy (REMS) for extended-release/long-acting (ER/LA) opioids in 2012 and mandated that prescribers receive ER/LA opioid REMS education. Many states have required that prescribers complete mandatory REMS continuing medical education to maintain prescriptive privileges for scheduled medications (most opioids are FDA Schedule II). PCPs can obtain this education through online or live educational programs.

The 2018 FDA *opioid analgesic REMS,* in addition to ER/LA opioids, includes all immediate-release (IR) opioids used in outpatient settings that are not already covered by other REMS programs. The *FDA education blueprint for healthcare providers involved in the treatment and monitoring of patients with pain* (FDA blueprint)[79] requires that prescribers: know the basic principles of pain physiology; identify alternatives to opioids (multimodal, CAM therapies, non-opioid pharmacologic agents); utilize risk stratification and screening for patient selection for the trial of opioid therapy; recognize side effects and drug interactions; anticipate and mitigate AEs (respiratory depression and overdose); and be knowledgeable about dose selection, titration, and equianalgesic dosing using morphine milligram equivalents (MMEs). It also details the use of opioids in special populations (e.g. pregnant women and older persons) and requires updated, increased knowledge about the problem of addiction (opioid use disorder).

PCPs must be cognizant of the evidence indicating that even relatively short term use of opioids can result in their continued

use, reliance, and possible addiction. The FDA has explicitly stated that PCPs treating patients with pain should be knowledgeable about the basic elements of addiction medicine, such as the definition, neurobiology, and pharmacotherapy of addiction.

Because of its pejorative and negative connotations, the term addiction can lead to stigmatization or blaming of individuals. The *Diagnostic and Statistical Manual of Mental Disorders* fifth edition (DSM-V)[80] has modified the term addiction to substance use disorder (SUD); in the case of opioid abuse/addiction, the preferred term is opioid use disorder (OUD). The DSM-V criteria make a clear distinction between a patient who misuses an opioid analgesic (by taking it differently than prescribed) to manage pain versus one who abuses an opioid analgesic with the intent of getting high. It has been estimated that the prevalence of OUD in patients with chronic non-cancer pain (CNCP) on chronic opioid therapy in primary care settings is 3% to 26%.[79] A mnemonic for identifying SUD is the five C's: control (loss of), compulsive use, craving drug, continued use (despite evidence of use causing harm), and chronic problem.

Table 75.14 lists the criteria for OUD.

TABLE 75.14 Diagnostic Criteria—Opioid Use Disorder DSM-V

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
   1. Opioids are often taken in larger amounts or over a longer period than was intended.
   2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
   3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
   4. Craving, or a strong desire or urge to use opioids.
   5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
   6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
   7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
   8. Recurrent opioid use in situations in which it is physically hazardous.
   9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
   10. Tolerance, as defined by either of the following:[a]
      a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
      b. A markedly diminished effect with continued use of the same amount of an opioid.
   11. Withdrawal, as manifested by either of the following:[b]
      a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547–548).
      b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Specify if:
- In early remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).
- In sustained remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).

Specify if:
- On maintenance therapy: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.
- In a controlled environment: This additional specifier is used if the individual is in an environment where access to opioids is restricted.

[a]Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
[b]Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

CDC Guideline for Prescribing Opioids for Chronic Pain

The CDC guideline for prescribing opioids for chronic pain-United States 2016[81] was published to help guide the prescriptive use of opioids by PCPs. This was in direct response to estimates that prescriptions from PCPs account for approximately 50% of opioid pain medications dispensed. At the same time, PCPs reported having received insufficient training and acknowledged their concerns about medication misuse and addiction. The guideline was specifically directed at clinicians in outpatient settings who treat patients over the age of 18 with chronic pain (defined as lasting greater than three months or past the time of normal tissue healing). An important and sometimes overlooked caveat is that the CDC guideline recommendations were not intended to guide the care of patients receiving active cancer treatment, palliative care, and/or care at the end of life.

The 2016 CDC guideline updated a 2014 AHRQ-sponsored review that researched key questions regarding the effectiveness of long term opioid therapy, harms, and AEs, effectiveness of methods for initiation, titration and dosing, accuracy of prediction instruments, and effectiveness of REMS, and effects of prescribing opioids for acute pain on long term use. Please see Chapter 48 for a review of guideline development.

The CDC's literature review showed that the evidence for outcomes regarding long term opioid therapy for chronic pain was very limited, with insufficient evidence to determine long term benefits; of concern, it suggested an increased risk of serious harms that appears to be dose-dependent. Newer studies revealed additional harms of long term opioid therapy, including increased risk of androgen deficiency among men receiving IR opioids; increased risk of overdose among patients receiving methadone; increased risk of overdose with the initiation of opioid therapy with ER/LA opioids compared with an initiation with IR opioids, and increased risk of long term use of opioids when opioids are used for acute pain. Newer studies also revealed new information about the sensitivity and specificity of the Opioid Risk Tool (ORT), the Screener and Opioid Assessment for Patients in Pain (SOAPP-Revised), and the brief risk interview, illustrating insufficient accuracy of these screening tools. The guideline review revealed that more research is needed to understand the long term benefits versus risk of abuse and related outcomes, effectiveness of different opioid prescribing methods and risk mitigation strategies, and accuracy of risk prediction instruments.

Therefore the CDC made 12 recommendations for safe opioid prescribing:

1. Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic treatment and non-opioid pharmacologic therapy as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.
4. When starting opioid therapy for chronic pain, clinicians should prescribe IR opioids instead of extended release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage.
6. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to greater than or equal to (≥) 50 MME per day, and should avoid increasing dosage to ≥90 MME per day or carefully justify a decision to titrate to ≥90 MME per day.
7. Long term opioid use often begins with the treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of IR opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
8. Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or dose escalation. Providers should evaluate the benefits and harms of continued therapy with patients every three months or more frequently. If the benefits do not outweigh the harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and discontinue opioids.
9. Before starting and periodically during the continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms.
10. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors increase the risk for opioid overdose, such as a history of overdose, history of a SUD, or higher opioid dosages (≥50 MME), are present.
11. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving high opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months.
12. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications and other controlled prescription drugs and illicit drugs.
13. Clinicians should avoid prescribing opioid pain medication for patients receiving benzodiazepines whenever possible.
14. Clinicians should offer or arrange evidence based treatment (usually medication assisted treatment with buprenorphine or methadone combined with behavioral therapies) for patients with OUD.

The CDC guideline faced criticism by pain advocacy groups over the risk of underprescribing for patients with chronic non-cancer pain and reports of insurers placing caps on both the number of pills and dosages of opioids prescribed. These unfortunate concerns reflect a lack of understanding of the original purpose of the guideline, which was intended to assist PCPs in their decision-making; it was not intended to constrain individual clinical practice patterns or dictate insurance policy. The goal was and remains the safe use of opioid analgesia by PCPs to protect patients and the public. Additionally, the guideline clearly states that it is directed at the treatment of patients with chronic non-cancer pain, and its recommendations do not apply to those living with active cancer or who are receiving palliative care for serious, life-limiting illness and/or at the end of life.[84]

Table 75.15 lists CDC guideline-congruent steps for initiating opioids.

The following caveats regarding opioid dosing were dosing included in the CDC guideline:

Higher dosages of opioids are associated with a higher risk of overdose and death; even relatively low dosages (20–50 MME per day) can increase risk. Higher dosages have not been shown to reduce pain over the long term.

Dosages at or above 50 MME/day increase risks for overdose by at least two times the risk at less than 20 MME/day.

TABLE 75.15 Initiating Opioid Therapy, Congruent With CDC Guideline

Begin a therapeutic trial with an immediate release (IR) opioid
Prescribe the lowest effective dosage
Use caution at any dosage, but particularly when: Increasing dosage to ≥50 morphine milligram equivalents (MME)/day Undertaking opioid rotation (switching from one to another opioid) Up-titrating the dose of an existing opioid
Carefully justify a decision to titrate dosage to ≥90 MME/day
Always include dosing instructions, including daily maximum
Be aware of interindividual variability of response
Have Patient-Prescriber Agreement (PPA), baseline urine drug test (UDT), and informed consent in place
Co-prescribe naloxone (if indicated) and bowel regimen
Re-evaluate risks/benefits within one to four weeks (could be as soon as three to five days) of initiation or dose escalation
Re-evaluate risks/benefits every three months; if benefits do not outweigh harms, optimize other therapies and work to taper and discontinue

Source: CO*RE-REMS program. Available at: www.core-rems.org.

Patients prescribed higher opioid dosages are at higher risk of overdose death. In a national sample of Veterans Health Administration patients with chronic pain receiving opioids from 2004–2009, patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce the risk of overdose.[81]

While perhaps an oversimplification of the approach to opioid prescribing, it may be useful to remember the geriatric adage regarding medication dosing, "start low and go slow." However, when treating pain, the adage may be modified to "start low but go." The latter statement acknowledges the need for caution and safe prescribing while also calling for frequent reassessment to determine the need for dose titration (up or down), rotation to another opioid, or additional interventions as indicated.

Table 75.16 lists recommended starting dosages for opioids.

TABLE 75.16 Opioid Dosages

Drug	Recommended Starting Dose	Comments
Hydrocodone	2.5–5 mg q4–6 h	Dose limited by non-opioid in combination-dose varies by product
Hydromorphone	1–2 mg q3–4 h	For breakthrough pain or around the clock dosing
Morphine Immediate release (IR) Sustained release (SR)	2.5–10 mg q4 h 15 mg q8–24 h	SR scheduling is product specific. Usually started after initial dose determined by IR. Toxic metabolites may limit usefulness with a high dose.
Methadone		Use ONLY by experienced clinicians
Oxycodone Immediate release Controlled release	 2.5–5 mg q4–6 h 10 mg q12 h	Significant interaction with food & alcohol
Tapentadol	50 mg PO q4–65 h	Dual action; may have a lower risk of gastrointestinal side effects vs. comparator opioids
Tramadol	12.5–25 mg q4–6 h	Dual action
Transdermal buprenorphine	5 mcg/h patch q7 days	A good option for older adults with dementia
Transdermal fentanyl	12–25 mcg/h patch q72 h	After the dose is determined by IR, the peak is 18–24 h. Duration 48-96 h

AGS panel on pharmacological management of persistent pain in older persons. *J Am Geriatr Soc.* 2009;57(8):1331–1346.

Pergolizzi JV, et al. Safety of buprenorphine transdermal system in the management of pain in older adults. *Postgrad Med.* 2017;129(1) 92–101.

Recognizing that there are differences in benefit, risk, and expected outcomes between patients with CNCP and those who are suffering from cancer pain or receiving palliative care and/or hospice services, prescribers of opioids should be aware of and ready to offer anticipatory guidance for opioid side effects. Patients whose pain is because of severe, life-limiting illness may be willing to tolerate or mitigate some side effects of opioids to obtain the needed level of analgesia. Thus for certain patients, PCPs may elect to treat side effects in the short term to achieve the longer term pain management goals, e.g. administering antihistamines to mitigate opioid-induced itching or antiemetics for nausea. All patients prescribed opioid therapy must also be counseled to maintain adequate fluid intake and take laxatives as needed since constipation is a ubiquitous side effect of opioid use that, left untreated, can lead to impaction/obstruction or, in severe cases, intestinal rupture. Generally, stool softeners alone are inadequate, especially if the patient is not taking fluids well; laxatives such as sennosides are preferred to ensure adequate laxation.

Table 75.17 lists common opioid side effects and AEs.

Besides the recommendations noted in Tables 75.14 and 75.15, and similarly to the 2018 FDA blueprint, the CDC guideline recommends using IR opioids when initiating therapy at the lowest possible dose for the shortest time necessary to achieve adequate analgesia. When opioids are needed for acute pain, PCPs should prescribe no more than needed. ER/LA opioids should not be prescribed for acute pain. Whenever opioids are required as treatment for pain, frequent follow up, and re-evaluation are recommended to assess the risk of harm. Suppose there are concerns for medication AEs, misuse, abuse, or suspicion for the development of OUD. In that case, clinicians are advised to carefully reduce the dose, continue to taper, and if needed, discontinue prescribing and make appropriate referrals for psychiatric/psychologic and/or medication assisted treatment.[82]

TABLE 75.17 Common Opioid Side Effects and Adverse Events

Respiratory depression: most serious
Opioid-induced constipation: most common, necessitates adequate fluid intake and co-prescribing stimulant laxatives
Sexual dysfunction and other endocrine abnormalities
Tolerance, physical dependence, hyperalgesia
Allergic reactions
Sedation, drowsiness, cognitive impairment
Risk for falls and fractures
Sweating, miosis, urinary retention
Hypogonadism
Myoclonus (twitching or jerking)
Addiction in vulnerable patients
Overdose and death

Decision to Refer Patients for Pain Management

Some PCPs decide to opt out of opioid prescribing because of the risks involved or who feel unprepared or unable to manage patients with OUD. However, every PCP will be called upon to treat patients who may truly benefit from opioid therapy. This includes but is not limited to patients with cancer-related pain and those for whom non-opioid pharmacologic options are contraindicated and/or provide inadequate analgesia, i.e. patients with multiple comorbidities such as CAD, diabetes, and chronic kidney or liver disease. It is also true that patients with OUD may require pain management for illness, surgery, or injury. If prescribing opioid therapy is beyond the PCP's level of training, knowledge, experience, and comfort, referrals to other providers with expertise in pain management or palliative medicine are most appropriate. Consultants for opioid pain management may include anesthesiologists, geriatricians (for the care of older adults with chronic pain), neurologists, physiatrists, and others. It is important not to conflate palliative care with hospice; not all patients who receive palliative pain management are hospice appropriate while, on the other hand, all patients who have enrolled in the hospice benefit will receive palliative care.[83] Palliative care focuses on symptom management (e.g. pain, fatigue, nausea, depression, anxiety, drowsiness, anorexia, constipation, dyspnea, secretions). PCPs are well-positioned to evaluate symptom complexes and to seek palliative care consultation. Referrals for palliative care are appropriate early in the course of any serious or life-limiting illness since early referrals may offer the best opportunity for favorable outcomes.

As noted in the introduction to this chapter, PCPs should develop a broad network of community resources to assist with the care of patients with pain. Several chapters discuss the role of these specialists in collaborative care for patients with pain. Also, see Chapter 44 (Geriatric Pain Management) and 82 (Pain Management at the End of Life and Home Care for the Terminally Ill Patient), which cover vital professional competencies for all PCPs.

Table 75.18 lists useful clinical resources for locating specialists for pain management and addiction treatment.

TABLE 75.18 Opioid Prescribing and Addiction Medicine Resources

American Society of Addiction Medicine: https://asam.ps.membersuite.com/directory/SeachDirectory_Criteria.aspx
https://www.asam.org/resources/resource-links

Substance Abuse and Mental Health Services Administration (SAMHSA): https://findtreatment.samhsa.gov/locator
Additional info: https://www.samhsa.gov/find-help/treatment

American Association of Addiction Psychiatrists: https://www.aaap.org/patients/find-a-specialist/

National Institute on Drug Abuse (NIDA): https://www.drugabuse.gov/

Providers' Clinical Support System for Opioid Therapies and Medication Assisted Treatment (PCSS): https://pcssnow.org/

Primary Care Goals for Pain Management

PCPs strive to partner with patients to set reasonable, achievable pain management goals. This necessitates a commitment to shared decision making with the recognition that while complete elimination of pain is usually not possible, it may be minimized so that quality of life, physical function, and psychosocial function are maintained. Besides pain reduction, the plan of care should include goals such as overall level of comfort, improved physical function and activity, improved interpersonal and social interactions, and improved mood. Utilizing functional rather than numeric treatment targets will enable the clinician, patient, and caregivers to assess meaningful progress toward these goals.

A useful mnemonic (similar to the Five C's for SUD) for assessing progress toward pain management goals is the five A's: analgesia (pain relief); activity/function (measured by the performance of ADLs); AEs (drug interactions, side effects); aberrant/problematic behaviors (abuse, misuse, diversion, addiction); and affect (mood).[79] A sixth "A" may be added to signify the clinician's response: action. Action represents the steps taken by the PCP, patient, and/or patient caregivers, based upon the assessment, to modify and improve the pain treatment plan of care. Table 75.19 lists the five A's and five C's.

A balance between the benefits and risks of therapeutic interventions is sought. To this end, patients should be enlisted in their self-care by recruiting personal skills that can help sustain treatment benefits rather than expecting that the clinician will "fix" them. Thus multimodal therapy coordinated by the primary care PCMH is ideal. Multimodal care incorporates nonpharmacologic and pharmacologic treatments that engage the skills of other providers to assist the patient in achieving analgesic and functional goals.

Patient involvement in their own pain management strategy involves information sharing and collaboration to identify realistic expectations and clear, achievable goals. Numerous factors may cause under-or overtreatment of pain, such as pain expectations based on prior pain experience, lack of knowledge or misinformation about pain and its treatment, and underreporting of pain. These may be minimized through an ongoing therapeutic relationship with a trusted PCP. Involving patients in the pain management planning process allows PCPs to clarify the goals of care and increases the likelihood of treatment adherence and the most favorable outcome possible.

TABLE 75.19 Monitoring Pain and Substance Use Disorder

Pain: Five A's	SUD: Five C's
Analgesia	Control, loss of
Activity/function	Compulsive use
Aberrant behavior	Craving drug
Adverse events	Continued use
Affect	Chronic problem

Source: CO*RE-REMS program, www.core-rems.org.

Key Points

- PCPs are the first contact and provide the initial evaluation for 65% of patients presenting with pain; they often become the sole providers for these patients.
- An ongoing therapeutic relationship between patients and their PCP medical home facilitates an interdisciplinary, multimodal, and comprehensive approach for resolving pain.
- LBP is a common pain presentation in primary care, so PCPs must have a fundamental understanding of the approach to its diagnosis and management.
- When evaluating LBP, a focused History and Physical (H&P) should identify the pain as belonging to one of three categories: red flag condition needing prompt treatment or where specific treatment exists; spinal stenosis or radiculopathy; or non-specific back pain. Avoid initial imaging unless a serious condition is suspected.
- PCPs should be knowledgeable regarding psychosocial factors that might suggest a higher risk of developing chronic pain and/or long term disability.
- Nonpharmacologic and non-opioid pharmacologic treatment options are the foundation for pain management in primary care.
- As many as one in four patients receiving long term opioid therapy in primary care settings struggle with OUD.
- CDC guideline recommendations for prescribing opioids for chronic pain include:
  Nonpharmacologic therapy & nonopioid pharmacologic therapy are preferred for treating chronic pain.
  Opioid therapy should be considered ONLY if expected benefits for both pain AND function are anticipated to outweigh risks to the patient. Opioids should never be the only form of treatment.
  Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.
- Multimodal pain management includes nonpharmacologic, complementary, and alternative medicine techniques, non-opioid and opioid pharmacologic therapy when indicated. Interdisciplinary collaboration with other providers is key to developing a comprehensive pain management strategy.
- PCPs should strive to involve patients in their own pain management strategy through clear communication and information-giving, shared decision making, and a commitment to an iterative process of reassessment and revision of the treatment plan that aims for enhanced quality of life and improved physical and psychosocial function.

Suggested Readings

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76

Pain Management in the Emergency Department

ANDREW K. CHANG

The management and treatment of the pain in the emergency department (ED) is unique from that experienced in other medical settings. Not only is pain often acute as opposed to chronic, but it is often unexpected and sudden. In addition, the type of painful conditions seen in the ED may respond differently to different types of treatments, such as the pain from a migraine versus the pain from a kidney stone. In these and other ways, the acute pain that is seen in the ED is different from the acute pain seen postoperatively, the latter of which is both expected and planned for.

Acute pain generally lasts less than seven days but can extend up to 30 days,[1] and in some cases can become chronic. Therefore emergency physicians are challenged to provide adequate pain relief, improve quality of life, and improve function while simultaneously trying to minimize adverse effects, including mitigation of the risk of addiction from the use of opioids, both in the ED and upon ED discharge.

Prevalence and Assessment of Pain in the ED

Pain is one of the most common reasons for patients to come to the ED.[2] The prevalence of pain among ED patients is approximately 45% based on cross-sectional data from the National Hospital Ambulatory Medical Care Survey, though the percentage of patients reporting severe pain increased from 25% in 2003 to 40% in 2008.[3]

Since the ED serves as a fail-safe mechanism for our fragmented healthcare system, chronic pain patients also present to the ED with acute exacerbations of their chronic pain. Extrapolating the results of a national telephone survey of 500 patients suggests that 34 million adults with chronic or recurrent pain visit the ED at least once every two years. Of this group, 43%, or 15 million, experience recurrent pain, while 57%, or 19 million, have underlying chronic pain syndromes.[4] The number of chronic pain patients visiting the ED has likely increased because some patients have had their opioid prescriptions suddenly reduced because of physicians' responses to the opioid epidemic.

Notwithstanding the issue of providing compassionate care, pain that is not acknowledged and managed appropriately can cause anxiety, depression, sleep disturbances, increased oxygen demands with the potential for end-organ ischemia, and even decreased movement, which can lead to an increased risk of venous thrombosis.[5] Failure to recognize and treat pain may also result in dissatisfaction with medical care, hostility toward medical staff, unscheduled return visits to the ED, delayed return to full function, and an increased risk of litigation.[6]

Pain is inherently subjective and inevitably complex, with each patient experiencing pain and suffering as an individual. As physicians, we assess our patients' pain indirectly and sometimes with skepticism. The validity of patient self-reports is often questioned and attempts to "objectify" the pain experience are sought, but no such biomarkers exist. In contrast, patients themselves, especially older adults, may be reluctant to report pain presence and intensity. This may result from low expectations of obtaining pain relief, fear of analgesic side effects, and a notion that pain is to be expected as part of the underlying disease or from medical treatments. In addition, some patients have a fear of addiction when prescribed opioids or fear the stigma associated with opioid use, including from a single dose of intravenous opioids for acute severe pain in the ED.

Pain assessment can be difficult in the ED, where time frames are often compressed, and therefore simpler assessment tools are generally preferred. Although far from perfect, the two most commonly used are the 11 point verbal numeric rating scale, in which pain is rated on a scale of 0 (no pain) to 10 (worst possible pain), and the verbal descriptor scale, in which pain is categorized as none, mild, moderate, and severe. These scales are also preferred by cognitively intact elderly ED patients.[7] No matter the specific pain scale used, assessments should be repeated after therapeutic interventions. Simply asking the patient the question, "Do you want more pain medication?" may be an alternative way of judging whether adequate pain relief has been obtained since individual patients have different thresholds of acceptable pain and may balance pain severity against side effects, such as nausea and sleepiness.[8] A non-numeric yes or no question may also be easier to comprehend among mildly confused patients, older adults, and those distracted by the severity of their pain.[8]

The Problem of Balancing Undertreatment of Pain and the Risk of Addiction

In 1989, Wilson and Pendleton coined the term "oligoanalgesia" in ED patients after performing a chart review of 200 ED patients.[9] This and subsequent studies found that analgesics were underused in the treatment of pain in ED patients in a significant proportion of patients.[10–12] A few years later, pain became known as the "fifth vital sign,"[13] and relieving pain became a national priority adopted by various societies, including The Joint Commission, the Institute of Medicine, and the now defunct American

Pain Society. As a result of these and other efforts, the amount of prescription opioids prescribed and sold in the United States quadrupled from 1999–2010.[14] Not surprisingly, the number of opioid overdose deaths also quadrupled.[14] Something had to be done though in some ways the pendulum may be swinging back too far to the other side, an example of which is the abandonment of some chronic pain patients.[15]

Although some patients may decline opioid analgesics because of concerns about addiction, the ED is also frequently targeted by patients addicted to opioids. Professional discussions of pain in the ED often center on concerns of being duped by patients who fabricate symptoms to obtain opioids, so-called drug-seeking behavior. Strategies to help with chronic pain patients demanding opioids in the ED are listed in Box 76.1.

Emergency physicians frequently struggle to balance appropriate relief of acute severe pain and prevent addiction to opioids. In managing pain complaints, emergency physicians are responsible for beneficence and nonmaleficence. They must treat pain and ameliorate suffering while minimizing the extent to which their decisions enable substance abuse and increase the supply of prescription opioids available for abuse by the general public. Fortunately, certain tools, such as online state prescription monitoring programs, can aid emergency physicians in differentiating appropriate and problematic requests for opioid analgesics.[16]

Pain Treatment

Effective pain management involves both pharmacologic and nonpharmacologic modalities. A recent systematic review on acute pain was published by the Agency for Healthcare Research and Quality.[17] Simply asking about pain and validating patients' reports of pain has a potent effect on patients' satisfaction with ED pain management. In one study, patient satisfaction with pain management was predicted more strongly by the perception that ED staff asked about pain than the actual administration of an analgesic.[18] Other modalities such as reassuring the patient that pain will be addressed, immobilizing and elevating injured extremities, and providing quiet, darkened rooms for patients with migraine headaches are essential aspects of quality pain management that can result in decreased amounts and use of opioids.

Analgesics may be administered by various routes. However, most analgesics are administered in the ED either orally or parenterally. Oral therapies are most commonly used in less severe cases because they are convenient and inexpensive for patients who can tolerate oral intake. When pain is severe, analgesics need to be given more urgently and ideally titrated to effect. The intravenous (IV) rather than intramuscular (IM) route is preferred in the ED setting. IM injections are painful, do not allow for titration, have unpredictable absorption, and can result in a slow onset of analgesic effect. Unless IV access is elusive, there are few situations to recommend the IM route. More recently, alternative delivery routes for the administration of pain medications have been described in the ED setting, including nebulized[19] and intranasal[20] fentanyl.

In general, it is inappropriate to delay analgesic use until a diagnosis has been made. In the case of acute abdominal pain, a large number of studies find no deleterious effect of intravenous opioid therapy on the ability of clinicians to make appropriate diagnoses.[21]

• Box 76.1 Strategies for the Chronic Pain Patient in the Emergency Department

- Validate patient's pain and frustration/fear/other emotions: "I know that you're in pain and you're worried."
- Set clear limits when responding to requests for intravenous (IV) opioids that are not indicated: "Our standard for all patients is to not give IV medication for people who are able to take pills. Oral pain medication will give you more steady pain control, and IV pain medication will wear off sooner."
- For patients who state that only IV opioid works: "I'm really sorry you feel that way. This sounds like it is terrible for you. I understand how it must be frustrating to understand why we are saying no to more opioids, but we care about your safety. I know there are ways we can work together so that you feel better."
- Do not abandon the patient but commit to treating with non-opioid measures: "I believe that you have pain, and I want to continue to work with you to treat the pain with other approaches."
- Use risk/benefit language: "The risks of these opioids are higher than the benefits for you."
- Be empathetic when it is time to deny or stop opioids: "This must be very difficult for you. Medical research does not support this type of pain medication, and it is simply not safe for you in the long run." "It may seem in the short run that opioids help, but they are not the best approach and can make your pain and problems worse over time."

Specific Treatment Modalities

A wide variety of analgesics are used in emergency medicine practice. In a 20 ED site survey, a total of 735 doses of 24 different analgesics were administered to 506 patients receiving analgesics while in the ED. The majority of analgesics administered were opioids (59%), with morphine being the most commonly used analgesic (20%), followed by ibuprofen (17%).21 Since the publication of this study in 2007, however, policy changes have been instituted in an attempt to de-emphasize the use of opioids in response to the opioid epidemic. The rescheduling of hydrocodone from Schedule III to Schedule II, which prevented refills and required a hardcopy prescription, is just one example.[22]

Non-opioids

Non-opioids include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and salicylates. In general, non-opioid agents exhibit an analgesic ceiling effect and cannot be titrated to effect. This limits their usefulness in the setting of severe or fluctuating pain; however, they can be considered as adjunctive therapy to opioids or combined in place of opioid therapy.[23]

Acetaminophen is indicated for mild to moderate pain and is often combined with opioid agents. Acetaminophen, unlike NSAIDs, has no antiplatelet activity or anti-inflammatory effect. Although a great deal of attention has been paid to acetaminophen hepatotoxicity, especially in the setting of chronic malnutrition, alcoholism, or liver disease, such concerns are generally not applicable in the ED setting where single or limited dosing is the general practice.

NSAIDs, including salicylates, inhibit prostaglandin synthesis by interfering with cyclooxygenase (COX) enzymes. Unlike acetaminophen, they also have an anti-inflammatory effect and are generally thought to be more potent than acetaminophen in their analgesic effect. However, they have more relevant adverse effects, including platelet dysfunction, increased risk of gastrointestinal bleeding, and increased risk of renal injury. Although NSAIDs are included in the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults,[24] most experts agree that single dose

use in the ED and/or short-term use after ED discharge is generally thought to be safe even in this population. Thus NSAIDs represent an important non-opioid analgesic in the ED setting.

Combination non-opioids, such as ibuprofen and acetaminophen, have also been studied in the ED. In one study of 416 non-elderly adult ED patients presenting with acute extremity injury requiring imaging, patients were randomized to receive one of four analgesics: oxycodone/acetaminophen, hydrocodone/acetaminophen, codeine/acetaminophen, or ibuprofen/acetaminophen. Pain scores were assessed at baseline, 1 and 2 h. There was no difference in improvement in pain scores among the four groups. There was also no difference in a subanalysis of patients who had documented fractures on radiographs and initial 10/10 pain score severity.[25] This suggests that combination non-opioids are a reasonable alternative to managing the pain from acute extremity injuries in most patients seen in the ED. However, patients should be informed that 4 grams is the daily maximum recommended amount of acetaminophen per day, with the makers of Tylenol recommending an even lower dose of 3 grams per day. Since the natural history of extremity injuries is to improve with immobilization and rest, it makes intuitive sense that the same non-opioid combination analgesics would also provide pain relief on par to opioids upon ED discharge. Since some patients who are prescribed an opioid will become addicted to an opioid, if emergency physicians can decrease the number of patients exposed to an opioid by using an alternative treatment such as that described above, then the number of people becoming addicted to prescription opioids should decrease. It is also important to remember that just because something might be generally true does not mean it applies to every patient. In other words, the lack of a difference in the four groups of the study mentioned above is on average, meaning that an individual patient might receive better pain relief with a particular analgesic, including an opioid.

Sub-Dissociative Ketamine

Several recent ED-based studies suggest a role of IV ketamine (a non-opioid) given in sub-dissociative doses (0.1–0.3 mg/kg over 10-15 min) either alone or as an adjunct to other analgesics in the management of acute pain.[26,27] However, patients can develop feelings of unreality and disorientation, although emergent reactions are rare.

IV Lidocaine

IV lidocaine has been shown to have efficacy in central pain syndromes and neuropathic pain, as well as opioid-sparing effects in the postoperative setting.[28] However, its use in the ED is not well defined primarily because of a lack of high quality studies.[29]

Opioids

Opioid combination analgesics are commonly used for moderate to severe pain in the ED. Although the opioid component in these agents does not exhibit ceiling analgesic effects, the non-opioid component dose is limited; thus one cannot titrate these analgesics. The convenience of combination therapy must be balanced against this limitation. Hydrocodone and oxycodone combination oral agents are most commonly used in the ED. Codeine is less commonly used because of the perception of less analgesic effect and concerns of variable metabolism, with some being poor metabolizers (and hence have little analgesic effect) and others hypermetabolizers (risking opioid overdose and respiratory depression).

If a patient's level of pain has been deemed severe enough to require an opioid upon ED discharge, it does not matter which one is chosen based on a series of ED studies that compared three commonly prescribed opioids (oxycodone/acetaminophen, hydrocodone/acetaminophen, and codeine/acetaminophen) against each other and found no clinically or statistically significant differences among them.[30–32]

Tramadol is also sometimes used in the ED because of its perception of having a decreased potential for abuse and respiratory depression. It is important to understand that although the risk may be less than that of traditional opioids, there remains a real risk for addiction. Its mechanism of action is unclear, with the tramadol component binding weakly to opioid receptors and inhibiting the reuptake of both norepinephrine and serotonin. One recent study using data from the Drug Abuse Warning Network concluded that tramadol combined with other drugs that depress the central nervous system (e.g. alcohol, benzodiazepines, other opioids) can enhance the sedative effects of tramadol, and caution should be exercised, especially in older adults.[33]

Opioids remain the mainstay of ED treatment for severe pain, and intravenous (IV) morphine is the standard treatment. Morphine 0.1 mg/kg as an initial bolus has been found to be safe but may not be adequate to effect pain relief.[34] If contraindicated because of allergy or other sensitivity, IV hydromorphone or IV fentanyl may be substituted for IV morphine. These opioids can be rapidly titrated to control severe pain. IV fentanyl has the advantage of being relatively short acting and is preferred in the setting of multiple trauma, head injury, and potential hemodynamic instability.

Hydromorphone is a potent opioid that has also been studied in the ED setting. The "1+1" hydromorphone rapid titration protocol administers 1 mg IV hydromorphone followed by an optional second 1 mg IV dose 15 min later based on patients' response to the question, "Do you want more pain medication?" In one study, this protocol provided adequate analgesia for 77% of patients within 15 min and 96% of ED patients within 1 h.[35] In an ED randomized clinical trial comparing the "1+1" hydromorphone protocol against usual care, in which the usual care group received an IV opioid, the "1+1" protocol was found to be statistically superior and at least as clinically efficacious and safe as traditional physician-driven treatment, with nine out of ten patients receiving satisfactory pain control within 1 h.[36] These same researchers then developed the "half and half" hydromorphone protocol for older adults (0.5 mg IV hydromorphone followed by an optional second dose of 0.5 mg IV hydromorphone based on response to the question, "Do you want more pain medication?") and demonstrated comparable pain relief to usual care but with lower mean initial doses of opioids at baseline and lower total opioids at 1 h.[37]

Most EDs have eliminated the use of meperidine because of its metabolism to normeperidine, a toxic metabolite causing central excitation and seizures, and its contraindication in patients taking monoamine oxidase inhibitors. The availability of other opioid agents of equal efficacy with fewer contraindications and fewer adverse effects argues against its continued use.

There is a current opioid epidemic in the United States, with Americans consuming 99% of the world's hydrocodone and 80% of the world's oxycodone. Therefore efforts to decrease the prescribing of opioids have become increasingly common, including the Centers for Disease Control (CDC) guidelines for Prescribing

Opioids for Chronic Pain published in 2016.[38] As the title of the publication states, the guidelines were mainly intended for patients with chronic pain; however, one of the 12 guidelines was relevant to acute pain and emergency medicine: "When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed." A recent survey of emergency physicians suggested that 12 tablets represents a 3 day supply while 28 tablets represents a 7 day supply for both younger adults and the elderly.[39]

Recent studies suggest that the contribution of emergency medicine to the opioid epidemic is limited, with emergency medicine accounting for only 4% of opioid prescriptions in 2012 in the United States.[40] Nevertheless, EDs had already begun to decrease their opioid prescribing, and various local and state guidelines were published prior to the release of the CDC guidelines. An example is the New York City ED Discharge Opioid Prescribing Guidelines that was released in early 2013.[41] This guideline gave nine recommendations for the management of patients with acute or chronic non-cancer pain discharged from an ED (Box 76.2). As of 2017, 17 states had ED opioid prescribing guidelines, with 67 recommendations around limiting prescriptions for opioids.[42]

•Box 76.2 New York City Emergency Department Discharge Opioid Prescribing Guidelines in the Management of Patients With Acute or Chronic Non-Cancer Pain (https://www1.nyc.gov/assets/doh/downloads/pdf/basas/opioid-prescribing-guidelines.pdf)

1. Short acting opioid for acute pain only when the severity of pain is reasonably assumed to warrant their use
2. Start with the lowest possible effective dose
3. Prescribe no more than a short course for acute pain. Most patients require no more than three days.
4. Assess for opioid misuse or addiction using targeted history, validated screening tools, and prescription data monitoring programs
5. Avoid initiating treatment with long-acting or extended release opioid analgesics
6. Address exacerbations of chronic or recurrent pain conditions with non-opioid analgesics, nonpharmacologic therapies, and/or referral to specialists for follow up, all as clinically appropriate
7. Avoid when possible prescribing opioids to patients currently taking benzodiazepines and/or other opioids.
8. Attempt to confirm with treating physician the validity of lost, stolen, or destroyed prescriptions. If considered appropriate, replace the prescription only with a one to two day supply.
9. Provide information on the risks of overdose and dependence/addiction, safe storage, and proper disposal of unused medications.

TABLE 76.1 Nonpharmacologic Treatments in the ED

Physical (physical therapy, osteopathic manipulation, mobilization)
Direct (heat/ice, acupuncture, transcutaneous electrical nerve stimulation, deep breathing, ultrasound)
Indirect (music therapy, aromatherapy, hypnosis, guided imagery)
Psychosocial (cognitive behavioral therapy, verbal suggestion, family support)
Education (oral advice, pamphlet, video)

Patient-Controlled Analgesia

The use of patient-controlled analgesia (PCA) has been studied in the ED, though a recent pragmatic trial of 366 patients found no advantage over usual care.[43] Nonetheless, in the setting of high demands on nursing resources, PCAs could serve to ensure adequate pain treatment.

Adjunctive Therapies and Nonpharmacologic Treatments

Given the opioid epidemic, there has been a renewed interest in the use of non-opioid analgesic adjunctive therapies and nonpharmacologic treatments of pain in the ED and after ED discharge (Table 76.1). A recent meta-analysis of 56 studies of nonpharmacologic pain interventions found that most were often effective in reducing pain in the ED though most studies were small in number.[44]

Nerve blocks have been shown to provide localized pain relief, improved door-to-analgesic times, and lowered doses of analgesics. They can be used as a stand-alone treatment or as part of a multimodal analgesic regimen. Ultrasound-guided femoral nerve blocks in particular have been shown to provide adequate pain relief in patients presenting with an acute hip fracture.[45]

Medication Assisted Therapy (MAT) in the ED

Because the ED is the only access point for care for many people, there has been a focus to start initiating MAT in the ED. A 2015 randomized clinical trial found that buprenorphine initiation in the ED is feasible.[46] In a diverse group of opioid-dependent patients, ED-initiated buprenorphine with primary care office-based follow up for ongoing treatment resulted in 78% of individuals engaged in treatment at 30 days. This compares to 37% of those referred to treatment and 45% of those who received a brief intervention who were still engaged in treatment at 30 days.[46]

MAT in the ED setting is primarily in the form of administering and prescribing buprenorphine and/or buprenorphine/naloxone, the latter of which is known by the trade names Suboxone and Zubsolv. Other MAT therapies, such as extended-release injections of naltrexone, are not currently commonly used in the ED setting.

Conclusion

The pain seen in EDs is often more acute and severe than that seen in other medical settings. Therefore emergency physicians are challenged to provide adequate pain relief for a wide variety of conditions, many of which require the use of opioids, while minimizing the extent to which their decisions enable substance abuse and increase the supply of prescription opioids available for abuse the general public. Given the current and ongoing opioid epidemic, there has been a renewed interest in the use of non-opioid analgesic adjunctive therapies and non-pharmacologic treatments of pain in the ED and after ED discharge, though many of these studies are limited by small sizes. EDs are also beginning to treat opioid use disorder with medication assisted therapies, such as combination buprenorphine and naloxone.

Key Points

- Failure to recognize and treat pain may cause unnecessary increases in anxiety and delayed return to function among ED patients.
- Consider short acting opioid analgesic for the treatment of acute pain only when the severity of the pain is reasonably assumed to warrant their use and prescribe a short course as most patients require no more than three days.
- Non-opioid and nonpharmacologic management, such as nerve blocks, should be considered whenever possible. Decreasing exposure of patients to opioids will decrease the chance of patients subsequently becoming addicted to opioids.
- NSAIDs are relatively contraindicated in older adults, though they are not likely to cause harm if used judiciously for a short time (e.g. three days or less), ideally in conjunction with a proton pump inhibitor for gastrointestinal prophylaxis and after assuring that the patient does not have acute or chronic renal failure.

Suggested Readings

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77

Management of Pain in Sickle Cell Disease

CARLTON D. DAMPIER

Sickle hemoglobin results from a replacement of glutamine with valine at the sixth amino acid position in the β-globin subunit. Molecules of this abnormal hemoglobin polymerize upon deoxygenation into long polymers that physically deform the erythrocyte into the characteristic sickle shape and ultimately obstruct blood flow.[1] This polymerization largely ceases when adult hemoglobin is present with sickle hemoglobin, the so-called sickle trait, or with high levels of fetal hemoglobin, resulting in relatively benign conditions. In contrast, this polymer formation is promoted to varying degrees by the co-occurrence of sickle hemoglobin with other inherited abnormal hemoglobin, such as hemoglobin C, D, E, or O^{arab}, or mutations that reduce the production of normal hemoglobin (thalassemia), resulting in sickling disorders of varying degrees of hemolytic severity.[2] Given the large phenotypic variability seen in this group of hemoglobin disorders, they collectively are often referred to as sickle cell disease (SCD).

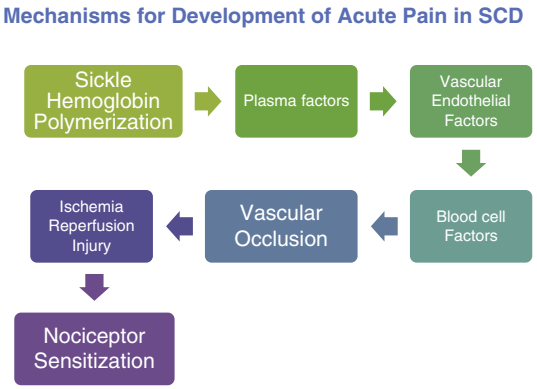
Recent whole genome sequencing suggests that the sickle mutation arose over 7,000 years ago, either in the Sahara or in west-central Africa.[3] Its prevalence was maintained and expanded in these areas by reproductive advantage as sickle trait provided some degree of protection from severe malaria.[4] Thus most of the 100,000 to 150,000 individuals with SCD in the United States trace their ethnic origins to Africa, the Middle East, or the Mediterranean where malaria was endemic; the slave trade to the Caribbean and South America also led to the spread of the sickle mutation to many individuals of Hispanic ethnicity.[5]

The pathophysiology of vaso-occlusive pain in SCD is quite complex (Fig. 77.1). Once deoxygenated, sickle hemoglobin undergoes a polymerization process that ultimately deforms the erythrocyte into the characteristic sickle shape. If the time required to complete this process, the "delay time," is longer than the time required for these erythrocytes to reach larger venous vessels, then vaso-occlusion will not occur.[6] Factors that slow the transit time of erythrocytes through the microcirculation will enhance the likelihood of vaso-occlusion, including changes in vascular tone and adhesion of erythrocytes, and other cellular elements, including leukocytes and platelets, to vascular endothelium altered by chronic hemolysis.[7] As part of this "vicious cycle" of sickling, the subsequent ischemic/reperfusion injury from initial vaso-occlusion results in the accumulation of endogenous mediators released from cells that reside within or infiltrate into the injured area (including mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts).[8] Collectively, these inflammatory mediators represent a wide array of signaling molecules, including neurotransmitters, peptides, eicosanoids, and related lipids, cytokines, and chemokines, which damage local nociceptive nerves leading to increased spontaneous firing that is perceived as acute pain.[9]

Although considerable further research is needed to confirm this process, the intense and repetitive nature of vaso-occlusive events and resulting chronic tissue/bone damage likely drive the development of chronic pain in adolescents and adults with SCD,[10] (Fig. 77.2) likely through a process termed *central sensitization,* which represents an activity- or use-dependent form of functional synaptic plasticity that can occur after intense, repetitive noxious stimuli.[11] Central sensitization with its augmented pain response and a symptom cluster denoting sleep difficulties, pain, affect, cognitive difficulties, and fatigue occurs by complex processes that change the response elicited by normal sensory inputs, including those that usually evoke innocuous sensations, resulting in the sensation of persistent pain.[12] Further changes in the pain experienced in chronic pain disorders occur because of anatomic and functional connectivity changes in various brain regions.[13]

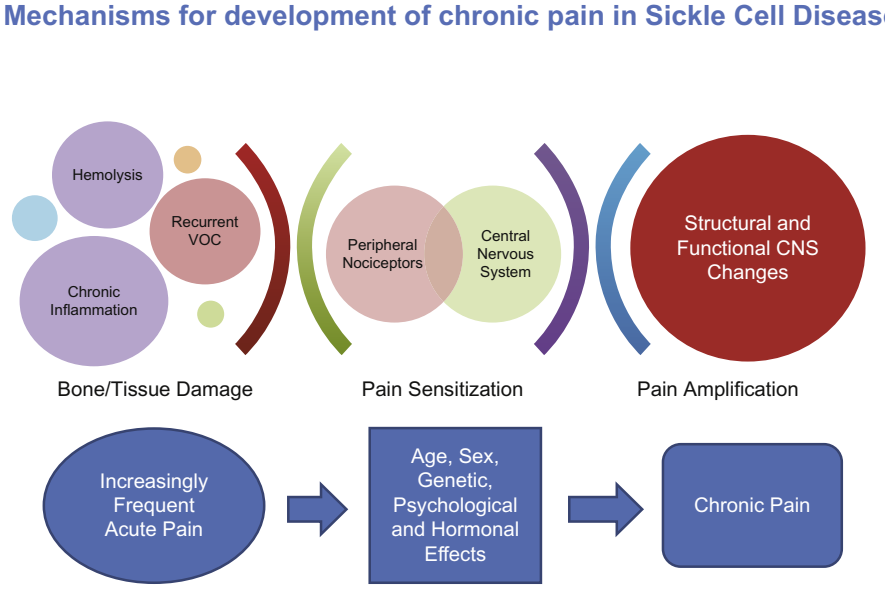
Epidemiology of Vaso-occlusive Pain

SCD is a relatively unique pain disorder, as pain can begin early in the first year of life as levels of fetal hemoglobin decline in susceptible individuals.[14] Most children reported to have pain in the first year of life have pain locations (hands/feet) and signs/symptoms (swelling or tenderness) consistent with dactylitis, often referred to as "hand-foot syndrome," which becomes progressively less prevalent in older children and rare after five to seven years of age.[15] Almost all children with SCD experience increasingly frequent pain throughout childhood and into adolescence and young adulthood.[16] However, most of these painful episodes are managed at home rather than in acute care settings.[17] Most episodes are relatively brief, typically two to three days, with the pain of moderate intensity located in a small number of body sites, usually the lower legs, back, and chest wall, with pain intensities often peaking in the late evening.[18,19] Some studies have suggested environmental triggers for these painful episodes, such as changes in weather,[20] or air quality,[21] while others have highlighted the role of stress,[22] potentially mediated by changes in vascular tone.[23]



• **Figure 77.1** Mechanisms for the development of acute pain in sickle cell disease.

young adults can experience acute left-upper-quadrant visceral pain from rapid enlargement of the splenic capsule consistent with acute splenic sequestration, an often life-threatening trapping of sickled erythrocytes and platelets in the spleen.[33] Almost all children with SCD will experience episodic right-upper-quadrant colicky abdominal pain and jaundice from cholelithiasis or bile duct obstruction and ultimately require cholecystectomy,[34] as chronic hemolysis results in bilirubin accumulation in the gallbladder and the subsequent production of pigment stones. Avascular necrosis in the vertebral column, shoulder, or hips can be a source of acute pain as well as chronic pain in adolescent and young adult patients,[35] who often respond to physical therapy for initial symptom management of hip pain; some patients, however, have progressive collapse, particularly in the head of the femur, that will ultimately require joint replacement for relief



• **Figure 77.2** Mechanisms for the development of chronic pain in SCD. *CNS*, Central nervous system; *SCD*, sickle cell disease; *VOC*, vaso-occlusive crisis.

A small number of children transition, often in their early adolescent years, from a pattern of sporadic episodes of brief acute pain to frequent, recurrent, acute pain with or without chronic pain. These individuals represent the majority of pediatric patients hospitalized for acute pain.[24] Pain is a more complex experience in adults with SCD, with features of both acute recurrent and chronic pain,[25,26] and is more often managed in an acute care setting compared to pain in children.[27] Sociodemographic, family, and disease characteristics and mental health issues are often comorbidities contributing to frequent healthcare utilization in SCD adults with hronic pain.[28,29] Detailed taxonomies describing acute pain,[30] and chronic pain in SCD have been recently published.[31]

Other Pain Etiologies in Sickle Cell Disease

Vaso-occlusive pain in SCD remains a clinical diagnosis as laboratory and imaging studies largely show non-specific increases in inflammatory markers and increased hemolysis.[32] Other pain syndromes distinct from vaso-occlusive episodes are not uncommon and always need to be considered when evaluating an individual with SCD and pain (Table 77.1). Children and, occasionally, of chronic pain or to improve physical functioning.[36] Although uncommon in the pediatric age group, leg ulcers, typically over the medial malleolus of either or both ankles, can be a source of considerable pain and disability, and are challenging to manage.[37] Headaches, as an isolated pain syndrome or as part of a vaso-occlusive event, can occur but are not well characterized.[38] Some have features characteristic of migraine headaches, others may be more typical of tension-type headaches, and a small number of individuals satisfy current diagnostic criteria for chronic daily headaches. The use of the triptan class of medications to treat migraine-like headaches in SCD individuals is contraindicated because of cardiovascular concerns.

Sickle Cell Disease Pain Management

Education Is the Foundation

A lifespan approach is most applicable for these sickling disorders, as pain will likely be experienced throughout childhood and adult life. A focus on the family is essential for children,[39,40] whereas adolescents must be encouraged and supported to accept progressively

TABLE 77.1 Pain Syndromes in Sickle Cell Disease Not Directly Involving Vaso-occlusion

Pain Syndrome	Typical Locations	Pain Characteristics
Acute splenic sequestration	Spleen	Acute visceral pain related to stretch of the splenic capsule from splenic enlargement
Splenic infarction	Spleen	Acute visceral pain from splenic infarction involving splenic tissue extending to splenic capsule
Acute bone infarction	Ribs, sternum, or long bones	Acute pain from necrosis of bone marrow
Avascular necrosis	Hips, shoulders, or vertebrae	Acute and chronic pain from progressive collapse of bone cortex related to persistent vascular compromise
Osteomyelitis	Any bone	Acute and chronic pain from bacterial infection of bone cortex or marrow, often related to chronic ischemia
Acute cholelithiasis	Gallbladder	Acute visceral pain from irritation or common bile duct obstruction by pigment gallstones
Leg ulcers	Medial or lateral ankles	Acute and chronic pain from ischemic damage to the skin and underlying soft tissue
Headache	Head	Acute or chronic headache pain with or without migrainous aura or characteristics

more responsibility for their own pain management so they can function appropriately in the adult healthcare system. Thus initial disease and pain management education involves parents and other caregivers for young children and broadens to include the school system in older children; finally, organized transition programs starting in early adolescence focus on self-management skill education.[41] Self-management skill development should include learning psychological approaches to pain management,[42] similar to other pediatric chronic pain disorders for which one meta-analysis indicated the superiority of cognitive behavioral interventions (multicomponent, relaxation, and biofeedback approaches) for pain management.[43]

Home Management: "It Takes a Village"

Several studies in children[44] and adults[25] suggest the preference to manage vaso-occlusive pain at home. The home setting is likely to be more comfortable for children and less disruptive to the families' normal activities and routines. Surprising to most healthcare providers, many SCD individuals avoid care in acute care settings, as they frequently encounter negative attitudes toward patients with SCD,[45] and a pervasive fear among healthcare providers of catering to opioid addiction, which often compromises analgesic therapy.[46] Successful home management requires a parent or other caregiver skilled in pain assessment and administration of appropriate analgesic medications. Extended family also is critical for psychological and physical support, as most pain episodes may last for several days and usually require around-the-clock medication for adequate management.[44] Support by trusted medical health professionals with experience in SCD and pain management also facilitates home management and appropriate emergency department utilization.[47]

Utilization of a biopsychosocial approach to pain management can be facilitated by engaging local complementary and alternative medicine practitioners and mental health professionals.[48] Reductions in post-procedure pain intensity scores suggest that acupuncture can be an effective adjuvant strategy for pain management in SCD.[49,50] Cognitive behavior[51,52] and mindfulness-based interventions have been evaluated in adolescents and adults.[53] In addition, guided imagery has been successfully used with younger children.[54] Clergy can also be helpful as several studies of caregivers of children with SCD have found that a large percentage of families use prayer and spiritual healing, in addition to medication to manage their child's pain at home.[55,56] Several eHealth and smartphone apps have also been developed to facilitate home pain management.[57–59]

Low potency analgesics, such as acetaminophen and ibuprofen, are recommended as initial therapy at the onset of typical vaso-occlusive pain and are often adequate for mild to moderate pain, particularly in younger children. These analgesics are often chosen out of concern for the adverse consequences of opioid analgesics and have the advantage of less sedation and subsequent disruption of age-appropriate activities. A substantial number of oral hydrocodone and oxycodone analgesics of varying potency, often in combination with acetaminophen, are available in liquid and tablet formulations for the management of more intense pain in children with SCD. Some shift away from the use of codeine containing analgesics because of pharmacogenetic issues of excessive toxicity or inadequate efficacy.[60] Although labeled dose amounts and frequency of potent oral opioid analgesics are usually prescribed, the enhanced hepatic and renal clearance of morphine in the SCD population,[61,62] and the potential impact of prevalent pharmacogenetic genotypes impacting morphine metabolism suggests that the dose and frequency of these opioids may need to be further individualized.[63] Increasing frequency of vaso-occlusive pain episodes is associated with increasing numbers of opioid prescriptions,[64,65] raising fears of opioid misuse in this population.[66] However, a review of death records shows no increase in opioid-related deaths in the sickle cell disease population during the current opioid epidemic.[67]

There have been few comparative studies of adjunctive non-opioid analgesic medications in this population. A study using pharmacy claims data suggested that pharmacologic treatments for sickle pain consisted mainly of NSAIDs and weak opioids.[68] Significantly more severe SCD patients, those with more than three yearly inpatient or emergency department (ED) visits for pain management, were prescribed more potent opioids, anti-depressants, or anti-convulsants. Prescription of both stronger opioids and anti-depressants or anti-convulsants were significantly associated with lower frequencies of acute sickle pain visits. Similarly, pregabalin provided some sustained reductions in pain intensity over a three month period in a small pilot study.[69] Further clinical trial data are needed in SCD individuals to support these observations and to establish comparative efficacy and safety data for various analgesic and anti-convulsant or anti-depressant combinations, particularly given increasing concern for neuropathic-like pain characteristics, particularly in adults.[70,71]

Management of Sickle Cell Disease Pain in the Acute Care Setting

Several studies have sought to identify characteristics of acute care utilization for sickle pain. A multicenter study across four United States cities enrolled all adults with SCD living within 60 miles (96.6 km) of a study site.[27] Twenty-one percent of participants had no acute care visits in the first 12 months of follow up, while 54% of subjects with hemoglobin SS disease and 46% with hemoglobin SC disease had three or more acute visits. Predictors of higher rates of acute care utilization included being unemployed, having chronic pain, being on chronic transfusion therapy, having a history of stroke, and being on disability or Medicaid. Similar findings have been observed in programs with day hospital/infusion centers with higher utilization associated with indicators of greater illness severity, more aggressive treatment for SCD, higher baseline opioid doses, higher socioeconomic status, greater pain related anxiety, and a history of psychiatric treatment.[29] A recent systematic review also examined risk factors for acute care utilization by pediatric patients.[72]

Comprehensive sickle pain treatment guidelines have been published by expert panels from both the National Institutes of Health[73] and the American Society of Hematology.[74] Early administration of opioid analgesics is recommended, and several ED analgesic protocols using intranasal analgesics have been developed to facilitate early analgesia.[75,76] An extensive learning collaborative model for the treatment of adults with acute sickle pain in emergency departments has been developed.[77] Implementation of this model has been shown to improve pain relief over the period of ED treatment.[78]

Intravenous doses of potent opioids, usually morphine or hydromorphone, are the typical initial treatment for vaso-occlusive pain in both adults and children, as all are assumed to have failed a course of oral analgesics at home prior to arrival in the ED. In some pediatric centers, intravenous nalbuphine is also used, as it is often associated with fewer complaints of nausea and pruritis,[79] but it is seldom used for SCD adults because it may precipitate opioid withdrawal symptoms in opioid tolerant individuals. Oral and subcutaneous routes of opioid administration are also an option for adults with limited intravenous access.[78] Administration of opioids by patient-controlled analgesia (PCA) devices is not a common practice in the ED, but where available, it allows more frequent dosing, which can be problematic in a busy ED.[80] The concurrent use of a parenteral NSAID, usually ketorolac, is a widespread clinical practice in the ED setting as an additional analgesic but are often reduced for renal insufficiency, which is not uncommon in adults with SCD.[81]

Sickle Cell Disease Pain Management in the Inpatient Setting

A snapshot of analgesic practice, across a large number of pediatric and adult hospitals that participated in an observational study of sickle pain management after hospitalization, documented the widespread use of opioid-based PCA.[82] Opioid doses varied over a wide range but appeared to be somewhat higher for individuals receiving PCA compared to scheduled opioid dosing, and for those receiving hydromorphone compared to morphine. A small clinical trial of opioid PCA dosing suggested that adult SCD individuals have a more rapid improvement in pain when using PCA largely delivered by continuous infusion rather than demand dosing, likely because individuals with severe pain had difficulty obtaining adequate pain relief with frequent demand doses early in the course of their hospitalization.[83] The importance of early analgesia is also supported by the observation that achieving an earlier maximum opioid dose was significantly associated with a shorter length of hospitalization for both frequent and infrequent pediatric sickle patients.[84]

Parenteral NSAIDs, usually ketorolac, are commonly used as an additional analgesic. Evidence of efficacy of other adjuvant analgesics for acute sickle pain is limited. Intravenous acetaminophen reduced pain intensity and provided some opioid-sparing effects in a recent single site study.[85] Refractory sickle pain that persists beyond three to five days can present a difficult management problem, particularly in adolescents and young adults. The use of concurrent low-dose ketamine infusions has been described for this situation in children,[86] and adults,[87] which were somewhat more effective in younger or males patients.[88] Use of intravenous lidocaine infusions have also been described,[89] but further research and clinical experience are needed.

Nausea, pruritus, and constipation are common opioid-related adverse effects during treatment for vaso-occlusive episodes[83] and require symptomatic management during the course of hospitalization, with constipation often being quite problematic.[90] The use of concurrent administration of low doses of an opioid antagonist (naloxone) has been shown in several small pediatric cohorts to ameliorate many central nervous systems (CNS) opioid-related symptoms without altering analgesia,[91,92] and it may be of particular importance in SCD where respiratory depression may increase the risk for symptomatic hypoxia and SCD pulmonary complications, such as acute chest syndrome. Common opioid-related adverse effects of nausea and constipation can be ameliorated by peripherally acting peripherally acting opioid antagonists,[93] but they have not been studied in SCD. Similar to its use for other critically ill patients,[94] transdermal or oral clonidine, an α2-adrenergic agonist, is often used in SCD adolescents and adults with prolonged hospitalizations and opioid exposure to reduce symptoms of opioid withdrawal after discharge, which otherwise might result in a subsequent readmission.

The use of nonpharmacologic techniques has been challenging in the inpatient setting, but a recent trial of an adapted yoga program has been piloted,[95] and approaches using virtual reality are encouraging.[96]

Management of Perioperative Pain in Sickle Cell Disease

Preoperative management of individuals with SCD relies on adequate, usually overnight, intravenous hydration and red blood cell transfusion if the hemoglobin is less than 10 grams/dL.[97] In some low-risk surgeries, transfusion may not be necessary, and in some high-risk surgeries, individuals with higher hemoglobin levels may require exchange transfusion.[98] Intraoperative management focuses on the prevention of sickling by maintaining adequate hydration, oxygenation, and ambient temperature. Effective pain control is a primary goal in the perioperative management of patients with SCD and may require additional analgesics compared to that used to treat other patients. For example, postoperative pain scores after laparoscopic cholecystectomy, one of the most common surgeries in SCD, were higher in SCD patients than in controls, and morphine consumption was more than double that compared to control children, as was the duration of PCA use.[99] SCD children also had a longer duration of postoperative hospital stay (3.4 ± 1.6 days versus 1.5 ± 0.5 days). These differences likely reflect alterations in pain perception from frequent vaso-occlusive episodes,[100] enhanced clearance of opioids,[62] and psychosocial variables.[101]

Management of Chronic Pain in Sickle Cell Disease: Largely Uncharted Territory

Chronic SCD pain has been defined as ongoing pain that was present, in one or more locations, on most days for more than six months.[31] Three subtypes of chronic SCD pain were proposed based on the presence or absence of either clinical signs or test results: (1) chronic SCD pain without contributory SCD complications, (2) chronic SCD pain with contributory SCD complications, and (3) chronic SCD pain with mixed pain types, if contributory SCD complications and pain are occurring in unrelated sites. The process for transition to chronic pain in pediatric SCD has been evaluated in a modest sized cohort follow up study.[102] Most participants who transitioned to chronic pain (80%) had episodic pain at baseline, suggesting a role for frequent and high pain intensity as suggested for several other chronic pain disorders.[103] Baseline psychosocial factors (i.e. higher functional disability, greater depressive symptoms, higher pain catastrophizing, and lower quality of life) were significantly associated with chronic pain at follow up, similar to other chronic pain syndromes.[104]

Data on the management of chronic daily sickle pain, which is likely prevalent in adolescents and young adults and associated with considerable disability,[26] is limited to a few case series or clinical trials. Currently, chronic pain management in SCD has largely relied on the use of long-acting opioid preparations,[16] or methadone,[105] sometimes using very large daily doses and putting these individuals at risk for opioid tolerance and opioid-induced hyperalgesia. Studies focusing on the U.S. population suggest that daily opioid usage is more frequent in individuals with comorbid psychological and psychiatric disorders,[106] and clinical experience suggests similar findings in the SCD population.[107] SCD chronic pain management strategies may benefit from extrapolations from other chronic pain syndromes where anti-depressants and anti-convulsants have proven track records of efficacy,[108] but further research and clinical experience are again needed before definitive treatment recommendations can be made. Adolescents and young adults with SCD who started on daily opioids should also receive concurrent psychosocial and psychiatric support, given the negative role that emotional, social, and psychiatric issues play in an individual's pain experience.[109] For example, establishing cognitive behavioral therapy care is associated with reductions in admissions for pain and length of stay for youth with chronic SCD pain, which may be partially supported by patient-reported improvements in functioning, coping, and lower pain intensity following CBT.[52]

An overview of the management of SCD is in Box 77.1.

• BOX 77.1 Management of Patients With Sickle Cell Disease

- Education
  - Self-management skill development
  - Cognitive behavioral interventions: multicomponent, relaxation, biofeedback
- Home care management
  - Parent or other caregiver trained in pain management
  - Psychological support from extended family
  - Timely emergency department utilization
- Analgesics
  - Low potency analgesics (acetaminophen, ibuprofen)
  - Oral hydrocodone
  - Non-opioids: nonsteroidal anti-inflammatory drugs (NSAIDs), pregabalin
- Acute care
  - Intravenous (IV) morphine, hydrocodone
  - IV Patient-controlled analgesia (PCA)
  - Parenteral NSAID (caution in patients with renal insufficiency)
- Inpatient setting
  - IV PCA with opioid
  - Parenteral NSAID
  - Ketamine infusion
  - Lidocaine infusion
  - Low-does naloxone (treatment of opioid adverse events)
  - Transdermal/oral clonidine
- Perioperative care
  - Preop IV hydration, blood transfusion per shared decision making of surgical team and patient
  - Intraoperative and postoperative: adequate hydration, oxygenation, ambient temperature, adequate pain control
- Chronic pain management
  - Long term opioid, e.g. methadone
  - Cognitive behavioral therapy
- Guidelines
  - National Institutes of Health[73]
  - American Society of Hematology[74]

Summary

SCD is unique as a lifelong pain disorder with features of acute recurrent pain in childhood that often transforms in adolescents or young adults into a chronic pain syndrome complicated by exacerbations of acute pain. Health providers and patients often have difficulty changing treatment goals and strategies during this transformation, which can be further complicated by transitioning from pediatric to adult healthcare systems. As with other chronic pain syndromes, mental health problems are frequent comorbidities; poverty and health disparities common in urban minority populations are additional challenges. Pain management optimally requires a multi-disciplinary team of hematologists, psychologists, physical therapists, alternative medicine practitioners, pain specialists, and addiction specialists. Further clinical collaborations are also important for expanding the evidence base for acute and chronic pain management in this population, which currently is distressingly limited. A further understanding of the pathophysiology of pain in this complex pain syndrome, likely driven by peripheral and central sensitization from repeated ischemic-reperfusion insults and chronic inflammation, could lead to the identification of new therapeutic targets and agents to ameliorate the pain and suffering currently experienced by individuals with SCD.

Key Points

- The pathophysiology of sickle vaso-occlusion in SCD involves intracellular polymer formation and related biochemical changes, a host of cellular interactions, and multiple inflammatory pathways, making the development of targeted therapeutics challenging.
- Pain from sickle vaso-occlusion likely represents acute nociceptor stimulation by inflammatory mediators from hypoxia and reperfusion injury, and peripheral and central sensitization from repeat episodes of severe pain.

- SCD is a relatively unique pain disorder, as pain can begin early in the first year of life, and almost all children with SCD experience increasingly frequent pain throughout childhood and into adolescence and young adulthood.
- Pain is a more complex experience in adults with SCD, with features of both acute recurrent and chronic pain.
- Mental health issues are often comorbidities contributing to frequent healthcare utilization in SCD adolescents and adults with chronic pain.
- Other pain syndromes distinct from vaso-occlusive episodes are not uncommon in children and adults with SCD, and they always need to be considered when evaluating an individual with SCD and pain.
- Low potency analgesics, such as acetaminophen and ibuprofen, are recommended as initial therapy at the onset of typical vaso-occlusive pain and are often adequate for mild to moderate pain, particularly in younger children. Oral hydrocodone and oxycodone analgesics, often in combination with acetaminophen, are available in liquid and tablet formulations for the management of more intense pain in children with SCD.
- Cognitive behavioral approaches—specifically deep breathing and progressive muscle relaxation, guided imagery, and calming self-talk—are effective psychological therapies for SCD pain in children and adolescents.
- Support by trusted medical health professionals with experience in SCD and pain management facilitates home management and appropriate ED utilization.
- Intravenous doses of potent opioids, usually morphine or hydromorphone, are the typical initial treatment for acute vaso-occlusive pain in both adults and children, as most have failed a course of oral analgesics at home prior to arrival in the ED.
- The concurrent use of a parenteral NSAID, usually ketorolac, is a widespread clinical practice in the ED setting as an additional analgesic, and it may have additional benefit as an anti-inflammatory agent.
- The efficacy of adjuvant analgesics for acute sickle pain has not been subjected to controlled trials, and refractory sickle pain is a difficult management problem, for which low-dose ketamine infusions are an encouraging therapeutic option for some patients.
- Chronic daily pain, which is likely prevalent in SCD adolescents and young adults, is largely managed with long-acting opioid preparations, but other analgesic and nonpharmacologic therapies are needed.
- Adolescents and young adults with SCD started on daily opioids should also receive concurrent psychosocial and psychiatric support and may benefit from anti-depressants and anti-convulsants, but further research and clinical experience are needed.

Suggested Readings

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Burn Pain

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Introduction

The management of pain related to burns presents a clinical challenge for providers given the complex physiology of injury, chronicity of pain, and the related psychological effects. Despite the variability in etiology, pathophysiology, and severity of burn injuries, treatment options for pain remain largely uniform despite the type of injury. So called traditional analgesic agents, including opioids, have been and remain a mainstay for the treatment of different types of burn pain. However, adjuvant agents and nonpharmacologic techniques also play important roles in the management of burn pain. Ideal management of patients with burn related pain involves a comprehensive and multi-disciplinary approach that involves pain management, psychological support, and nonpharmacologic therapy.[1]

Chronic pain related to burn injury is highly relevant and is a significant challenge for burn survivors. In a survey of 336 burn patients, 52% reported ongoing pain with an average duration of 11 years after their injury. Of these respondents, 66% reported pain so severe that it interfered with rehabilitation, and 45% reported interference in their daily life.[2] Although past attempts have been made to manage the complex pain associated with burn injuries, evidence-based treatment regimens and algorithms for burn pain management remain limited.[3] Current practice standards for burn pain management are inadequate, inconsistent, and mostly unchanged in many centers for over two decades, with opioid- and benzodiazepine-based regimens as the mainstay of therapy in the acute setting. This chapter will highlight the epidemiology of burns, the pathophysiology of burn injuries and phases of recovery, and options for pain management, including pharmacologic and nonpharmacologic options.

Epidemiology

Burn injuries represent a major public health concern. They represent the fourth most common type of trauma after traffic injuries, falls, and interpersonal violence worldwide. In 2004, approximately 11 million people sought medical care for burn related injuries globally. In the United States alone, 486,000 people sought care for burn injuries in 2016. The majority of burns are minor, involving less than 10% of the total body surface area. In 2016, the American Burn Association (ABA) documented that 40,000 patients were hospitalized with a burn injury.[4]

The ABA 2019 National Burn Repository of patients admitted to burn centers in the United States (approximately 220,000 burn cases from 2009–2018) revealed that 60% of patients were Caucasian, 20.6% were Black, 9.5% were Hispanic, and 2.5% were Asian. Men constitute most burn patients, accounting for 62% of cases treated at burn centers in the United States. The distribution of burn injury is bimodal, with high prevalence in the adult (16 years of age and older) and pediatric (0 to 15.9 years old) groups. Though, the majority of burns (56%) occur between ages 20 and 60 years. The two most common causes of burns, fire/flame (37%) and scald (29%), make up 66% of all burn etiologies, followed by contact with hot objects (9.1%), electrical (3.6%), and chemical (3.5%) burns.[5] The age of the person correlates with the type of injury, with scald burns occurring more frequently in children and flame-related burns more common in adults.[6]

Significant advances have been made in public health efforts to mitigate burn related injury in high-income nations, such as smoke detector systems, flame-retardant children's sleepwear, industrial innovations to avoid fire, and improvements in clinical care. However, low- and middle-income countries have yet to fully benefit from such advances. The World Health Organization estimates that over 300,000 people die from fire-related burn injuries each year. Over 95% of fire-related burns are in low- and middle-income nations.[7] Deaths related to fire are highest in South-East Asia (11.6 per 100,000 population per year), the Eastern Mediterranean (6.4 per 100,000 population per year), and Africa (6.1 deaths per 100,000 population per year).[7] With only one death per 100,000 population per year in high-income nations, fire-related mortality represents one of the largest discrepancies for any injury etiology. Moreover, burns are a major contributor to disability and disfigurement across the world, with fire-related burns accounting for ten million disability adjusted life years lost globally each year.[8]

Pathophysiology

Based on the location and extent of the insult, burn injury is a traumatic event that may result in a systematic inflammatory response affecting all organ systems.[6] At the molecular level, there is a massive activation of inflammatory mediators, including histamine, prostaglandins, thromboxane, bradykinin, serotonin, catecholamines, platelet aggregation factor, angiotensin II, vasopressin, oxygen radicals (superoxide, hydrogen peroxide, hydroxyl ion), and corticotrophin-releasing factor. At the cellular-level protein denaturation and coagulation, surrounding tissue hypoperfusion, capillary vasoconstriction occurs, where there may be disruption to structures deep to the skin (e.g. dermal tissue, muscle). Local responses to burn trauma can develop into a systemic response that

manifests as myocardial dysfunction, increased systemic vascular resistance, increased pulmonary vascular resistance, increased pulmonary capillary wedge pressure, organ ischemia, peripheral capillary leak (causing interstitial and pulmonary edema secondary to hypoproteinemia), and temperature dysregulation (from loss of body heat and increased evaporative water loss). In severe cases, the result may be fatal as a consequence of infection, respiratory distress, shock, or multiple organ failure.[6]

Phases of Burn Recovery

The appearance, presence of pain, and healing times of the different burn depths are shown in Table 78.1. Recovery from burn injuries can be broadly divided into four phases.[9] The first phase is the initial evaluation and resuscitation that occurs over one to three days post-injury. This is when the patient often requires large volume fluid resuscitation. The second phase is when the burn wounds are excised and temporarily closed with autografting or allografting of skin to accelerate the natural healing process. This generally occurs over weeks to months, depending on the size of the burn injury. The third phase occurs with definitive wound closure and reconstruction. Finally, the final stage of recovery is rehabilitation and reconstruction, which eventually leads to discharge and reintegration into society.[10]

Types of Pain in Burn Patients

Acute post-burn injury pain can be extremely challenging to treat, often necessitating aggressive use of opioids for analgesia. Burn depth, total body surface area affected, mechanism of injury, and various patient factors play a significant role in acute burn pain. Differences in the mechanism of burn injury may also alter the severity and complexity of pain experienced. For example, pain from a partial thickness (second degree) burn results from loss of dermis and epidermis exposing raw nerve fibers. In contrast, nerves are also burned with the upper skin layers in full thickness (third degree) burns, resulting in lower levels of acute pain.[11] Pain from burns maybe both nociceptive and neuropathic in origin.[12] Pain in burn patients can be divided into four different categories, which may intensify as tissues heal:

1. *Rest pain* - constant lower grade background pain
2. *Breakthrough pain* - intermittent, short duration, rapid onset/offset, sometimes excruciating pain in those with already established baseline pain control[13]
3. *Procedural pain* - short duration, greatest intensity, occurring with certain activities (i.e. wound cleaning, debridement, dressing changes, joint range of motion exercises)
4. *Psychogenic pain* - anticipatory pain in the absence of mechanical stimulation

Pain Management Options

Current treatment of burn pain necessitates a multimodal approach to improve the likelihood of effective post-burn pain management, using both pharmacologic and nonpharmacologic methods. Many pharmacologic agents (Table 78.2) are available to manage the various types of pain related to burn injuries. Because these have been presented in greater detail elsewhere in this text, we will only provide a cursory review of the various agents in a context appropriate for burn pain management.

Pharmacologic Analgesia

Opioids

Opioids including morphine, hydromorphone, and fentanyl have been the cornerstone of effective burn pain management for decades. They are widely available, can be administered by a variety of routes (e.g. oral [PO], intravenous [IV], transdermal), are inexpensive, and have a relatively ubiquitous familiarity among healthcare providers. In experimental studies utilizing burn injury, opioids (μ-receptor agonists) have been shown to produce antinociceptive effects– although there may be reduced efficacy of morphine antinociception in chronic burn injury.[14,15] Opioid doses required by patients in the acute phase of burn injury to control pain may require adjustment based on the severity of burn injury. For example, in a study of IV-PCA usage of patients with burn injury, Lin et al. showed a positive correlation between the percentage of total body surface area burned and VAS to morphine consumption. They also showed a trend of reduced morphine use with burn injury improvement. Additionally, they cite that given the subjectivity of burn related pain, specific opiate dosing guidelines are difficult, reporting that average morphine equivalents administered to the patient can range from 55 mg to 120 mg per day, based on the severity of burn.[16]

An early negative consequence of (and possibly result from) this rapid and massive dose escalation is the development of acute opioid tolerance. A later consequence of this opioid escalation may be opioid-induced hyperalgesia. Longer acting opioids, such as methadone, may mitigate or even reverse this acute tolerance and hyperalgesia, as might using other non-opioid analgesics, including ketamine, dextromethorphan, and clonidine.

TABLE 78.1 Features of Burn Depths, an Association of Pain, and Approximate Healing Times

Burn Depth		Appearance	Blistering	Sensation	Healing Time
Epidermal		– Red	None	Painful	Seven days
Partial Thickness	Superficial	– Pink w/ wet appearance – Brisk cap-refill	(+)	Painful	14 days
	Deep	– Pale/fixed red staining – Poor cap-refill	(+/–)	Painful or painless	21 days (+/–) burn excision & skin grafting
Full Thickness		– Leathery white or brown	None	None in the burned area (+/–) Pain at edges	Usually requires burn excision & skin grafting

Adapted from Gandhi M. et al. Management of pain in children with burns. *Int J Pediatrics.* 2010.[9]

TABLE 78.2 Pharmacologic Management of Burn Pain

Agents	Examples	Mechanism of Action	Administration
Opioids	Fentanyl, morphine, hydromorphone, buprenorphine, methadone, levorphanol	μ-R agonist	IV, PO, IM, TD
NMDA antagonists	Ketamine Dextromethorphan	Non-competitive NMDA-R antagonist	IV,
NSAIDs	Ketorolac Ibuprofen Meloxicam (available IV) APAP- this is not accurate- Acetaminophen is not an NSAID, nor does it derive its action via Cox 1 and Cox 2 inhibition- please place this in a separate agent box and review the appropriate mechanism of action/ available routes of administration	Cyclooxygenase (COX-1 and 2) inhibition	IV, PO, PR; intrathecal/ local (experimental)
Gabapentinoids	Gabapentin Pregabalin	Ca^{2+} channel blockade (α2δ-1 subunit-containing channels)	PO
Local anesthetics	Lidocaine Bupivacaine Ropivacaine	Na^{+}-channel blockade	IV (lidocaine), epidural/ intrathecal, perineural, TD
α2 Adrenergic agonists	Clonidine Dexmedetomidine	Central and peripheral α2-adrenergic blockade/ sympatholysis	IV (dexmedetomidine), PO
SNRI agonists	Tapentadol, tramadol, duloxetine	Serotonin and norepinephrine reuptake inhibitor activity	

APAP, N-acetyl-p-aminophenol/acetaminophen; *IM*, intramuscular; *IV*, intravenous; *NMDA*, N-methyl-D-aspartate; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PO*, per os; *PR*, per rectum; *TD*, transdermal.

Although opioids are an important modality for the treatment of burn pain, clinicians should be aware of the side effects (including respiratory depression, constipation, hyperalgesia) associated with their use in any patient. For burn patients, the immunosuppressant effects of opioids could theoretically lead to an increased risk of infectious complications during their acute hospital stay, although opioids should not be withheld in patients with burn related pain.[17]

Methadone is a unique opioid because of its receptor binding properties. It is both a μ-opioid and N-methyl-D-aspartate (NMDA)-receptor antagonist and also has serotonin and norepinephrine reuptake inhibitor properties. Administration can occur via oral, parenteral, and rectal routes. However, because of variable and unpredictable potency, dosing efficacy is dependent on chronicity. The long-acting analgesia provided by methadone makes this an ideal opioid for maintenance in burn pain management.[3] Further, the NMDA antagonist properties may be responsible for reducing or reversing opioid tolerance and hyperalgesia from other shorter-acting opioids, as well as modulating neuropathic pain. Methadone may be a viable option for some burn patients who are opioid-tolerant and have developed chronic neuropathic pain unrelieved by conventional pharmacotherapies.[18] An additional alternative to traditional opiate medications is levorphanol, a μ-opioid agonist. In a double-blinded trial of 81 patients, investigators compared low (0.15 mg) and high dose (0.75 mg) levorphanol for chronic neuropathic pain and noted that the high-strength levorphanol reduced pain by 36%, in contrast to a 21% reduction in the low-strength group.[19]

Fentanyl is a synthetic lipophilic opioid analog with high potency. These properties facilitate the rapid onset of action and quick redistribution from the central circulation. Lipophilicity allows for transmucosal absorption via nasal or buccal routes with rapid onset and peak effect similar to that achieved by IV administration. Although fentanyl is generally administered intravenously, it can be given orally, intranasally, and transdermally. These properties make this opioid a useful adjunct for procedural burn care activities, such as dressing changes and hydrotherapy.[20] The use of oral transmucosal fentanyl citrate and patient controlled intranasal fentanyl for procedural wound care in burns patients has been reported.[20,21]

NMDA Receptor Antagonists

NMDA antagonists such as ketamine and dextromethorphan are valuable agents for the treatment of burn pain as the NMDA receptor plays a central role in neuropathic pain processing and tolerance. In an experimental human study, ketamine significantly reduced the area of secondary hyperalgesia resulting from local first degree burn injury.[22] Similarly, dextromethorphan reduced the magnitude of secondary hyperalgesia from experimentally produced burn injuries.[23]

Ketamine is a non-competitive NMDA receptor antagonist with anti-hyperalgesia and anti-allodynia properties. It reduces

NMDA-R mediated central transmission and processing of pain, thereby inhibiting central windup. Thus there are many benefits to initiating ketamine early in the course of burn wound care. When administered with opioids, ketamine has synergistic effects with superior pain relief and reduced opioid consumption compared to placebo. When administered with opioids, ketamine appears to have a synergistic analgesic effect on experimentally induced windup-like pain in humans.[24,25] At analgesic doses, it has significantly less risk of respiratory depression and negligible psychomimetic or dissociative effects.[26] Analgesic maintenance dosing ranges from about 1 to 3 mcg/kg/min (or 0.05–0.15 mg/kg/h or 4–10 mg/h). Furthermore, there appears to be no risk of developing tolerance to the drug, even with an extended-duration infusion at analgesic doses.[27,28] A survey of 188 European burn centers noted that ketamine was preferred for analgesia in 12% and sedation in 13% of all substances used.[29] A systematic review of studies investigating intravenous ketamine as an analgesic agent for burn pain suggested that ketamine demonstrated analgesic efficacy for burn injuries with attenuation of secondary hyperalgesia and that no subjects withdrew from the studies as a result of ketamine-related side effects.[30] Delivery of ketamine via patient controlled analgesia for burn dressing changes has been reported.[31] Ketamine has been used for long term sedation and analgesia in burn patients.[27,31] Finally, ketamine may be an effective analgesic agent for painful procedures in pediatric burn patients.[32]

Dextromethorphan (DXM) is a non-competitive NMDA receptor antagonist that acts by reducing excitatory transmission of primary afferent pathways and is effective in managing challenging neuropathic/windup pain in patients who, for a variety of reasons, may be unable to receive ketamine. It has a reduced affinity for the NMDA receptor compared to ketamine and has a significant first-pass effect in the liver via CYP2D6 microsomal enzymes. Clinically, DXM has synergistic effects when administered with opioids and has superior analgesic and opioid-reducing effects when compared to placebo. The range of DXM doses used in published studies is 60 mg twice a day to 90 mg three times a day range. It is effective in 70% to 90% of patients but has been shown to have better efficacy at lower doses when coadministered with a CYP2D6-inhibitor such as quinidine. There are virtually no psychomimetic effects at the doses used clinically.[33] However, clinically, ketamine appears to be used more frequently than dextromethorphan.

Nonsteroidal Anti-inflammatory Agents (NSAIDs)

Analgesia from nonsteroidal anti-inflammatory drugs (NSAIDs) occurs by reducing inflammation and inflammatory mediators via cyclooxygenase-specific inhibition (COX-1 and COX-2). In the burn trauma population, NSAIDs may be useful adjuncts to help reduce the neurogenic inflammatory pain and fever associated with burns. However, in the acute setting, their use should be time- and dose-limited as they may present increased risks of bleeding from platelet dysfunction, gastric ulcers, and gastrointestinal bleeding from COX-1 inhibition in the setting of acute stress and renal dysfunction in the setting of reduced renal perfusion, especially in patients with larger total body surface area burns.[34] COX-2-specific inhibitors (i.e. celecoxib) may offer a better overall safety profile than non-specific COX-inhibitors like ibuprofen and ketorolac, but data in the burn patient population is lacking and needs to be better studied. NSAIDs may be especially useful for the treatment of burn pain as experimental studies suggest that intrathecal or local administration of NSAIDs may decrease post-burn hyperalgesia and reduce hypersensitivity in skin sensitized by ultraviolet burn.[35,36] Intravenous ketorolac administered to volunteers increased pressure pain tolerance threshold and attenuated secondary hyperalgesia from an experimental skin burn injury.[37] In addition, experimental animal studies suggest that NSAIDs may enhance tissue perfusion and reduce edema formation after burns.[38] There are few studies specifically examining NSAIDs or acetaminophen alone in the treatment of burn pain as the vast majority of these agents have been used as part of a multimodal approach to pain management in burn patients. A prospective, multicenter, randomized, double-blind trial evaluating intravenous ibuprofen for treatment of fever and pain in burn patients found that use of intravenous ibuprofen was associated with a significant reduction in fever and that use of the maximum daily recommended dose (800 mg every 6 h) over five days was well tolerated.[34] Finally, acetaminophen (also called paracetamol, or APAP) may be useful in the management of rest burn pain in children at doses in the 10 to 15 mg/kg/4 h range. It is available for administration via oral, rectal, and intravenous routes. In one observational study, 50% of children received only acetaminophen to control background pain.[39]

α2δ Agonists

The alpha two delta agonists (often referred to as gabapentinoids) *gabapentin* and *pregabalin* are lipophilic structural analogs of γ-aminobutyric acid (GABA) that bind to the α2δ-1 subunit of voltage gated calcium channels. In injured dorsal root ganglion neurons, gabapentin has been shown to selectively silence spontaneous discharges but failed to block the propagation of normal impulses.[40] In peripheral nerve injury, as occurs in burn trauma, gabapentin activates and enhances the efficacy and release of descending noradrenergic neuronal activity from the locus coeruleus. By using central neuronal plasticity, it induces more spinal noradrenaline release after nerve injury,[41] suppresses transmission of pain signals to the brain, and may facilitate a more natural sleep-like state in the acute setting owing to the upregulation of activity in the locus coeruleus.[42] Gabapentinoids may be potentially effective for the treatment of burn pain as experimental studies demonstrate that oral gabapentin (in humans) may decrease primary mechanical allodynia in acute inflammation following a thermal injury and that intrathecal gabapentin (in rats) may produce a dose-dependent reversal of thermal hyperalgesia evoked by mild thermal injury.[43,44]

Despite the potential benefits of gabapentinoids in the treatment of burn pain especially considering the presence of neuropathic pain in burn patients, few studies have actually been undertaken to examine the analgesic efficacy of this modality. One of the few double-blind, randomized placebo-controlled trials examining the analgesic efficacy of pregabalin found that administration of pregabalin (up to 300 mg twice a day over 28 days) significantly reduced several aspects of the neuropathic pain and pain associated with procedures.[45] A relatively small retrospective review of pregabalin noted that 69% of patients in a burn outpatient clinic experienced some reduction in pain score after treatment with pregabalin.[46] However, a prospective, randomized, double-blinded, single center, placebo-controlled trial comparing pregabalin 300 mg, 600 mg, and placebo for noncritical partial and full thickness burn injuries showed no statistically significant differences in pain scores and opiate consumption.[47]

Observational data suggest that gabapentin may be useful in reducing neuropathic burn related pain as administration of gabapentin resulted in a rapid reduction in the severity of the neuropathic burn pain and decreased opioid consumption.[48,49] Another potentially useful role for gabapentin is its use for the

treatment of post-burn pruritus in patients where pruritus is not relieved with antihistamines.[50]

Na^+-channel Blockers—Local Anesthetics

Sodium channel blockers such as local anesthetics have been shown to reduce primary and secondary hyperalgesia from experimental heat trauma in humans.[51] Human experimental studies indicate that intravenous lidocaine may attenuate longterm inflammation-induced tissue responses to thermal injury,[52] and has been shown to attenuate cytokine-induced cell injury in endothelial and vascular smooth muscle cells.[53] Local anesthetics for analgesia can be administered via nerve blocks or intravenously, in some cases.

Intravenous lidocaine has been used as an analgesic agent for postoperative pain control and the treatment of neuropathic pain. There is only one randomized controlled trial,[54] and a few observational reports describing the use of intravenous lidocaine for the treatment of burn pain.[55,56] The sole randomized controlled trial examined intravenous lidocaine (versus placebo) in 45 severe burn patients undergoing wound care procedures on two consecutive days. Subjects were randomized to either the intravenous lidocaine or control on the first dressing day and crossed over to the alternate treatment on the second dressing day. Although pain scores were significantly lower for lidocaine, there were no significant differences concerning opioid consumption or satisfaction.[54] A systematic Cochrane review was unable to recommend routine use of intravenous lidocaine in burn pain management at this time.[57]

Neuraxial and peripheral regional nerve blockade have been used as analgesic techniques in the treatment of postoperative pain. However, these techniques have not been widely used for the treatment of burn pain. Instead, a variety of single-injection regional analgesic techniques have been described in burn patients, typically for the purpose of reducing pain at skin graft donor sites.[58,59] One case report describes using double continuous peripheral nerve block catheters in a child after suffering a burn injury.[60,61] Despite the potential benefits that peripheral and neuraxial catheter blocks can offer, clinicians should be aware of the potential infectious complications associated with continuous regional analgesic techniques, especially if indwelling catheters are used for any duration.

α2-Adrenergic Agonists

Clonidine and *dexmedetomidine* are both selective central and peripheral α2-adrenergic agonists that act to decrease norepinephrine at presynaptic receptor sites thereby reducing autonomic outflow. Both drugs significantly reduce pain intensity and have a morphine-sparing effect.[62] Other potential benefits include anti-inflammatory effects, improved macrophage function, anti-apoptotic activity, reduced delirium, and reduced mortality by approximately ~70% for dexmedetomidine when compared to using benzodiazepines for sedation in critically ill patients.[63] Analgesic dosing for these agents depends on the route of administration. For clonidine, dosing regimens may include 2 to 5 mcg/kg PO, 0.1 to 0.3 mg/24 h TTD, or 30 mcg-300 mcg IV for procedural sedation in chronic opioid/chronic pain patients. It can potentially also be used in the neuraxial setting with intrathecal or epidural administration. Dexmedetomidine is given exclusively IV as an infusion at 0.2 to 1.0 mcg/kg/h. In terms of nociception, α2-adrenergic agonists may have a role in the prevention of pain. Experimental data suggest that α2-adrenoceptor-mediated mechanisms may be involved nociceptor sensitization to heat stimuli in normal skin and produce antinociceptive effects in a thermal hyperalgesia model.[64] Clinically, α2-adrenergic agonists may be used for analgesia and sedation in burn patients. A report of oral clonidine in a burn patient who had severe pain noted that administration of clonidine resulted in improved analgesia and sedation.[65] The addition of low-dose intravenous clonidine in a child with severe burns requiring large doses of morphine resulted in a significant decrease in morphine consumption with improvement in ventilatory, gastrointestinal, and psychological functions.[66] When administered to burn patients, dexmedetomidine is typically used for sedation for procedures or in critically ill mechanically ventilated patients.[67]

Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)

Tramadol and *tapentadol* are examples of SNRI that also have μ-receptor agonist activity. *Duloxetine* is an SNRI that has been used in the treatment of both subacute and chronic pain. Generally, SNRI drugs seem to modulate pain circuitry at both the spinal and supratentorial levels.[68] Furthermore, SNRIs have been shown to help improve deregulation of inflammatory markers typically indicated in pain states such as tumor necrosis factor and interleukin-6.[69]

Nonpharmacologic Analgesia

Pain perception can be altered through psychological, cognitive, emotional, and environmental factors.[70] Although management of burn pain is typically achieved primarily by pharmacologic agents, nonpharmacologic techniques (Table 78.3) may be particularly helpful in the treatment of burn pain especially considering the long term nature of rehabilitation and possible development of chronic pain and stress-related disorders. Therefore various nonpharmacologic modalities (e.g. cognitive therapies, relaxation techniques) have been examined although there are significant methodologic limitations in many available studies.

Virtual Reality

Virtual reality utilizes computer-simulated environments that primarily incorporate sight to simulate physical presence in an alternate environment. By incorporating input through multiple senses, including visual, auditory, and tactile, VR can lead participants' focus away from pain and into engaging the virtual world.[70] The application of virtual reality may be most useful during painful procedures and typically used in conjunction with pharmacologic analgesic agents (rather than as a sole modality for analgesia). By distracting a patient's attention from the real world

TABLE 78.3 Nonpharmacologic Management of Burn Pain

Method	Purported Mechanism of Action
Virtual Reality	Mostly visual distraction/decrease in processing of incoming nociceptive signals
Music Therapy	Auditory distraction/attenuation of stress response to pain
Relaxation Techniques	Behavioral management of anxiety, especially immediately pre-procedure/dressing changes

painful experiences (and possibly decreasing processing of incoming nociceptive signals), virtual reality may potentially reduce pain from procedures by approximately 35% to 50% with a corresponding decrease in pain related brain activity as documented by functional magnetic resonance imaging (fMRI).[71] There has been inconsistent data, though, in the efficacy of VR's role in pain reduction for burn patients. However, a 2018 systematic review and meta-analysis of 13 randomized controlled trials with 362 patients who underwent 627 burn dressing change or physical therapy sessions did show that compared to analgesics alone, VR in addition to analgesic medication achieved a greater reduction in pain intensity.[70]

Although virtual reality can be used for patients in any age group, this technique may be especially useful for pediatric patients.[72] For example, in a randomized control trial of 54 pediatric patients who underwent physical therapy for burn injury, patients reported significant decreases in perceived pain (27%–44%, $P < 0.05$) as well as improved affect ("fun") ($P < 0.001$) during VR.[73]

Despite its potential benefits, practical challenges remain to utilizing VR in the clinical setting. Depending on the type of virtual reality system used, three may be a significant time commitment from staff for implementation of such a system and prohibitive costs.[74]

Music Therapy

There is some evidence suggesting that the use of music may be of benefit in decreasing pain, especially during dressing changes or debridement procedures.[75,76] Music may attenuate some measures of the cognitive and physiologic component of the stress response with a lower heart rate and anxiety in subjects who listened to music versus those who did not.[77] A randomized control trial of 70 burn patients comparing standard therapy versus music intervention over five consecutive days of dressing changes showed significant reduction in pain and anxiety, though not in the morphine dosage used for both groups.[78] However, not all data have demonstrated a decrease in burn pain with music therapy,[79] and reporting guidelines for music-based interventions have been proposed.[80] Music therapy may be a valuable nonpharmacologic intervention for the treatment of procedural pain after burn injury.

Relaxation Techniques

Relaxation techniques (e.g. breathing relaxation techniques) may be a useful adjunct to pharmacologic agents for the treatment of burn as these techniques, in essence, do not increase patient risk, are easily mastered and implemented, and generally do not require expensive equipment.[81] A systematic review of simple relaxation techniques for burn pain was unable to definitively determine the efficacy of simple relaxation techniques for the treatment of burn pain. However, concentration on breathing, combined with jaw relaxation, was suggested to be the most promising technique.[82] Hypnosis has also shown potential benefit in patients with burn injury associated pain.[83]

Psychological factors have an influential role in pain perception and the management of patients with chronic pain. There is growing evidence for cognitive behavior therapy (CBT) as a meaningful treatment for chronic pain. In a study of 128 patients recovering from a burn injury, comparing group CBT to usual care, there was a substantial decline of general symptom severity and post-traumatic stress in the CBT group.[84]

Future research should address some of the methodologic limitations of currently available studies in this area and alternative modalities (i.e. electronic and group therapy) to improve access to delivery.

Summary

Pain associated with burn injuries can be complex and is best treated with a multimodal approach to analgesia. Because burn injuries can cause extensive damage, one needs to be aware that nociceptive and neuropathic agents should be utilized for optimal pain control. There are few large scale randomized controlled trials to guide our analgesic management for burn patients, and we currently are guided by our pathophysiologic understanding of the nociceptive processing of burn pain. Furthermore, nonpharmacologic modalities can also offer substantial pain relief and should be incorporated to successfully treat pain in burn patients.

Key Points

- In the United States alone, 486,000 people sought care for burn injuries in 2016, with over 10 million people seeking care for burn injuries worldwide.
- Modern day clinical burn injury care requires an aggressive multimodal and multi-disciplinary approach to effective post-burn pain management, using both pharmacologic and non-pharmacologic methods.
- Acute post-burn injury pain is often very severe and extremely challenging to treat, usually necessitating extreme doses of opioids for analgesia.
- Pain from burns may be both nociceptive and neuropathic in origin.
- Pain in burn patients can be divided into four different categories: rest pain, breakthrough pain, procedural pain, psychogenic pain.
- In experimental burn injury, opioids (μ-receptor agonists) have been shown to produce antinociceptive effects.
- Consequences of rapid and massive opioid dose escalation may include acute opioid tolerance and/or opioid-induced hyperalgesia.
- Longer acting opioids, such as methadone, may be a viable option for some burn patients who are opioid-tolerant and have developed neuropathic pain.
- Fentanyl is a useful adjunct for procedural burn care activities, such as dressing changes and hydrotherapy because of rapid onset of action and quick redistribution.
- NMDA antagonists such as ketamine and dextromethorphan may be valuable agents for the treatment of burn pain as the NMDA receptor plays a central role in neuropathic pain processing and tolerance.
- NSAIDs may be useful adjuncts to help reduce the neurogenic inflammatory pain and fever associated with burns.
- Gabapentinoids may be potentially effective for the treatment of burn pain since they decrease primary mechanical allodynia in acute inflammation following a thermal injury.
- Peripheral regional nerve blockade may be useful at reducing pain at skin graft donor site but should be used with care because of potential issues of infection.
- Dexmedetomidine may reduce mortality by approximately ~70% when compared to benzodiazepines for sedation in critically ill patients.
- Nonpharmacologic techniques, including cognitive therapies, relaxation techniques, music therapy, and virtual reality, may be particularly helpful in the treatment of burn pain.

Suggested Readings

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Pain Evaluation and Management in Patients With Limited Ability to Communicate Because of Dementia

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Pain is a subjective experience, and as such, its assessment typically relies heavily on patient self-report. However, in moderate to severe dementia, the ability to communicate verbally the subjective state of pain declines. Limited ability to communicate pain results in serious caregiver challenges in pain recognition and monitoring. It is, therefore, not surprising that despite its high prevalence in dementia,[1,2] pain is frequently undertreated in this population.[3,4] Morrison and Sui[5], for example, found that 76% of postoperative patients with dementia did not have standing orders for analgesia. Nonetheless, more recent research from Norway and Denmark suggests that the prevalence of pain undertreatment may be decreasing in those countries.[6,7]

Interestingly, researchers have failed to find significant correlations between nurses' estimates of long term care (LTC) resident pain and the administration of pain medications.[8] This is possibly because of enduring beliefs that pain is normal for frail older adults with dementia and thus should be endured. Moreover, recent research has shown that documentation of pain in LTC settings does not tend to reflect best practice standards. In an investigation involving several Australian facilities, Andrews et al.[9] showed that many pain episodes were not documented, and only a minority of episodes (22%) were associated with evidence-based assessments. Moreover, deficits in dosing patterns and appropriateness of pain medication have been identified for older adults in home care, including those with cognitive impairments.[10] Clinicians should be aware of such barriers to effective pain care and must take steps to mitigate these.

A significant concern that compounds the problem of pain undertreatment is that pain in dementia can lead to challenging responsive behaviors,[11] which, in turn, can be misattributed to psychiatric causes leading to treatment with psychotropic rather than analgesic medication.[12] Psychotropic medication may hasten death in this population[13] possibly by increasing the risk of stroke and falls.[14,15] Effective pain monitoring can reduce polypharmacy and psychotropic medication use.[16] Given potential adverse effects from pharmacologic modalities, nonpharmacologic pain management approaches (e.g. frequent repositioning, massage) also have an important role in the pain care of the dementia patient and should be considered the cornerstone of multimodal pain management in this population.

Pain Assessment Using Self-Report

Although dementia compromises linguistic and cognitive abilities in general, self-report tends to remain a valid indicator of pain in early to moderate stages of the dementia process.[17] A recent study of residents with cognitive impairment showed that less than half could self-report pain using a simple zero to ten numeric rating scale.[18] Weiner et al.[19] found that the mean Mini-Mental Status Examination (MMSE)[20] scores in two samples of older adults with cognitive impairments, who were able to self-report pain, ranged from 18.6 to 22. Those unable to self-report pain had MMSE scores with a range of 12 to 13.1, classified as having severe dementia. Chibnall and Tait[21] studied older adults with mean MMSE scores of 18 and found good support for the psychometric properties of simple self-report tools.

Interestingly, Ferrell et al.[22] demonstrated that 83% of research participants with an average MMSE score of 12 could complete at least one of four simple unidimensional pain assessment tools (i.e. The Present Pain Intensity Scale [PPI] of the McGill Pain Questionnaire [MPQ],[23] a verbal rating scale [VRS; involving four to six verbal descriptors indicative of different pain intensities], a 100 mm visual analog scale [VAS], the Rand Coop Chart[24] and the Memorial Pain Assessment Card subscale[25]; the two latter tools are not used commonly in this population), with the Pain Intensity Scale (PPI) of the MPQ[23] having the highest completion rates. The PPI is a zero to five scale that uses both numeric and verbal descriptors of pain intensity. The findings of Ferrell et al.[22] imply that it may be beneficial to attempt several different unidimensional self-report tools (e.g. a zero to ten pain intensity numeric rating scale [NRS] anchored by polar opposites such as "no pain" and "most pain," VRS, PPI) in older adults who have moderate dementia to determine which tool is the best suited for the individual patient.

Among the most commonly used pain self-report tools among younger adults is the horizontal visual analog scale (i.e. a 10 cm line anchored by the polar opposites "No Pain" and "Extreme Pain"). This scale, however, is not recommended for older adults because it has been associated with frequent unscorable responses in this population.[26] Nonetheless, better results have been demonstrated through the use of vertical analog scales.[27]

The Colored Analog Scale (CAS)[28] has also been used with some success in samples of persons with dementia. The CAS is usually presented on a rectangular piece of plastic that looks like a ruler. On one side, there is a shape that starts thin at the bottom and gradually increases in width, and deepens in color (from light pink to red) as one moves toward the top. There are "no pain" to "most pain" anchors at the top and bottom of the scale. The patient is asked to move a plastic guide to indicate the location on the scale that best describes his or her pain. The CAS was originally developed for young children with marginal self-report skills but has been used successfully in samples of older adults with mild to moderate dementia.[17] However, older adults with severe dementia are often unable to complete the tool.[29] Scherder and Bouma[27] suggested an approach that can be used to evaluate the patient's ability to comprehend the scale (e.g. asking the patient to point to the scale, point to the plastic glide, point to where the glide should be placed when there is no pain).

Although no test can determine with certainty the extent to which a patient can self-report pain effectively, a rule of thumb has been suggested based on the literature mentioned above.[17] Specifically, it would be reasonable to expect that an MMSE score of 18 or higher would indicate that a senior would likely be able to use unidimensional pain measures such as the zero to ten pain intensity NRS and the CAS. In contrast, those with MMSE scores below 12 would be more likely to have difficulty with the tools. Nonetheless, self-report should be attempted in all cases as some older adults with low MMSE scores may still be able to provide valid self-report. Based on the literature and our direct experience in clinical settings, we recommend that the NRS, PPI, and/or CAS be attempted. Where scales are presented visually (e.g. the CAS or the VRS),[30] it is important to ensure that large fonts are used to compensate for visual impairments that become more common in older age groups. While multidimensional pain assessment scales (e.g. the short version of the Geriatric Pain Measure [GPM],[31,32] which assesses disengagement because of pain and pain with ambulation in addition to pain intensity), have been shown to be useful with older adults who are cognitively intact, research is needed on the development of suitable multidimensional pain assessment tools for older adults with moderate to advanced dementia.

Pain Assessment Using Observational Assessment Tools

Given the limited ability of many older adults with moderate to severe dementia to effectively self-report pain, there has been a proliferation of observational measures designed to assess pain in this population (see Hadjistavropoulos et al.[33] for a review of various available tools). Many of these measures have limited validity evidence, but some have been studied more and have a substantial evidence base behind them. Among the most studied measures are the Pain Assessment in Advanced Dementia (PAINAD)[34] and the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC and PACSLAC-II) scales.[35,36]

The PAINAD consists of five items (Breathing, Negative Vocalization, Facial Expression, Body Language and Consolability), with each rated on a zero to two scale based on specific criteria. For example, Negative Vocalization is rated as follows: 0 = Normal; 1 = Occasional moan or groan, low-level speech with a negative or disapproving quality; 2 = Repeated troubled calling out, loud moaning or groaning, crying. The PAINAD has demonstrated good psychometric properties, including the ability to differentiate painful situations from non-pain related states,[37,38] and been translated in several languages.[39–41]

Comprehensively covering all pain assessment domains recommended by the American Geriatrics Society,[42,43] the original PACSLAC scale[36] consisted of 60 items organized into the following categories (Facial Expression, Activity Body Movement, Social Mood Personality, and Other, which includes physiologic changes, eating/sleeping changes and vocal behaviors). Each item is scored as present or absent, and the scale usually takes less than 5 min to complete. The PACSLAC has been shown to have good internal consistency and to differentiate pain related from non-pain related experiences.[36–38] When used regularly in an LTC environment, the PACSLAC was shown to result in reduced pain levels (as assessed by LTC staff), increased use of *pro re nata* analgesic medication, and reduced nurse stress. In a study of nursing staff who used the PACSLAC, the PAINAD, and the Doloplus[44,45] (which is a validated tool that has been used widely in France with English translations available from the developers' website),[46] Zwakhalen et al.[37] demonstrated that, while all three tools had good psychometric properties, nursing staff expressed a preference for the PACSLAC. Notably, the PACSLAC has been found to account for more variance in differentiating pain from non-pain related states than other commonly used observational pain assessment tools, even when several other tools were used in combination.[38] The PACSLAC has been translated into several languages.[47–49]

Despite the strong psychometric properties of the PACSLAC[36–38,50,51], a newer version, the PACSLAC-II, was developed.[35] The 31 item PACSLAC-II was intended to be a briefer scale that would maintain comprehensive coverage of the pain assessment domains recommended by the American Geriatrics Society,[43] would exclude many items that frequently overlap with delirium, and would emphasize items informed by previous investigations, including laboratory research (e.g. specific facial responses that are frequently associated with pain). The psychometric properties of the PACSLAC-II have been supported.[35,52,53] The PACSLAC-II has been found to account for more variance in differentiating pain related from non-pain related states than other commonly used tools, including the original PACSLAC, even when several other tools were used in combination.[35] Moreover, regular use of the PACSLAC-II in an LTC environment, combined with physician involvement, was shown to lead to reductions in benzodiazepines compared to a control group of patients whose caregivers did not use the PACSLAC-II regularly.[16] The reductions in benzodiazepines may have been because of a better understanding of agitated behaviors that could have resulted from pain instead of another source of distress. Other research has suggested that, under professional guidance and direction, laypersons (e.g. informal caregivers) should be able to complete the PACSLAC-II and the PAINAD in a valid fashion allowing for the provision of important pain assessment information by family members to health professionals.[54] More recently, an app version of the PACSLAC-II, with the capability of graphing patient scores over time (allowing LTC staff to observe deviations from patients' regular pattern of scores), was developed and evaluated with good results.[55] The PACSLAC-II has been translated into French, Farsi, and other languages.[52,56] A copy of the PACSLAC-II has been included as an Appendix of this chapter.

Recently, Kunz et al.[57] developed a 15 item "meta-tool" for pain assessment in "impaired cognition, especially dementia," the Pain Assessment in Impaired Cognition-15 (PAIC15) using items from preexisting scales such as the PACSLAC and the PAINAD. Tools

that were published after 2012 (e.g. the PACSLAC-II) were not considered. The selection of items and tools was based on expert consensus and studies that evaluated some of the psychometric properties of candidate items.[58] Although promising, a limitation of this work is that a direct comparison of the validity of the PAIC15 with that of other well validated tools in assessing pain in dementia was not reported. Pending such a direct comparison, the clinical value added because of the PAIC15 introduction remains to be determined through additional research.

On occasion, cutoff scores for observational pain assessment tools have been proposed in the literature.[59] However, we have explicitly argued against such practice on the following grounds: a score on an observational assessment tool would vary as a function of situational and personal factors such as duration of observation (e.g. longer observation periods would likely result in higher scores than short observation periods) and the nature of the dementing illness (e.g. dementias primarily affecting the frontal lobes would like result in more disinhibited pain responses compared to dementias primarily affecting the posterior part of the brain). Other factors, such as facial paralysis or mobility limitations, would also affect the repertoire of pain behaviors being displayed. The wide variety of factors, besides pain, that can affect scores on observational tools implies that the use of universally applicable cutoff scores would be problematic. As an alternative to the use of cutoff scores, it has been suggested that an idiographic approach be adopted wherein each patient is assessed regularly over time, and clinicians look for fluctuations in the patient's typical pattern of scores.[17] Unexpected increases or decreases from such a pattern of scores would imply changes in status.

Other Dimensions of the Pain Experience

The clinician needs to be cognizant that persistent pain affects a wide variety of quality of life dimensions, including mood and level of agitation. As such, a thorough assessment of the persistent pain would also involve consideration of such dimensions. Useful psychometric evaluation tools for mood, agitation, and quality of life, specifically designed for people with moderate to severe dementia, rely on input from knowledgeable informants and include the Cornell Depression in Dementia,[60] Alzheimer Disease Related Quality of Life-Revised tool,[61] and the Cohen-Mansfield Agitation Inventory.[62]

It is also important to acknowledge that multiple medical and psychological (particularly depressive) conditions and syndromes contribute to the pain experience (e.g. multiple pain diagnoses, sleep disturbance, musculoskeletal pain, chronic wounds, neuropathy), delirium[63,64] and that the pain itself is a result of a multifactorial pathway.[65] Assessing and addressing multimorbidity, often through careful review of the medical record, will be important for effective and safe pain management.

A Clinical Approach to Assessment of the Older Adult With Limited Ability to Communicate Because of Dementia

Several guidelines and consensus groups have described clinical approaches designed to optimize and facilitate the assessment of patients with dementia.[66,67] These approaches have much in common.[68] A general approach to the pain assessment of older adults with cognitive impairments, reflecting key points presented in various guidelines, is outlined in Table 79.1.

One of the most recent and up-to-date guidelines for pain assessment in the patient unable to self-report is the 2019 Position Statement of the American Society for Pain Management Nursing.[67] The statement emphasizes the following general recommendations: 1) be aware of potential causes of pain; 2) attempt self-report; 3) observe patient behaviors; 4) solicit proxy reporting of pain behaviors and activity changes; and 5) attempt an analgesic trial. The position statement recommends using validated assessment tools as appropriate (minimizing the emphasis on vital signs for pain assessment, regularity of pain assessment), and follow up assessments following the intervention. When soliciting proxy reports of pain, clinicians should note that proxy and patient reports of pain do not always correspond.[69] Proxy reports should be considered in the context of all other sources of information about the patient, including results of the physical examination. Moreover, in many instances, nonpharmacologic interventions may be appropriate prior to attempting an analgesic trial.

Because of concerns about limited personnel and other resources that characterize many LTC facilities, a group of geriatric pain and public policy experts recommended a feasible model of pain assessment for LTC facilities.[70] Specifically, they outlined the following recommendations:

Every LTC resident should be assessed for pain on admission and at least once a week thereafter using a validated tool. Assessments would need to be more frequent when pain is suspected and/or if symptoms appear to escalate.

A treatment plan should be documented in the chart within 24 h for patients with suspected moderate to severe pain. Depending on the circumstances, the treatment plan can be simple (e.g. administer acetaminophen) or more thorough following a medical examination.

24 h following treatment plan implementation, side effects of treatment should be evaluated and addressed.

Pain should be re-evaluated within 24 h of treatment plan implementation.

Research has demonstrated that stakeholders (e.g. front line health professionals, LTC administrators) assessed these guidelines as feasible, desirable, and appropriate.[71] Moreover, the feasibility of implementation of the aforementioned four clinical guidelines, with no significant added resources, has been demonstrated[55,72] although the sustainability of such guidelines over time would require ongoing management support. The impact of such guideline implementation on patient outcomes deserves further study.

Nonpharmacologic Pain Management

Research in nonpharmacologic pain management for patients with dementia has been extremely limited. Evidence suggests that physical therapy and physical exercise interventions are effective in this population for specific types of musculoskeletal problems.[73,74] Yet physical therapy is not always available to those who need it in LTC facilities. Sensory stimulation has also been found to be a viable option for nonpharmacologic pain management in dementia, and group psychosocial interventions have demonstrated larger effect sizes than individual approaches.[75]

A wide variety of comfort measures (e.g. soothing music, more frequent repositioning of patients with mobility limitations) can also be used, but evidence suggests that these measures are underutilized.[76] Systematic investigations of comfort measures (e.g. listening to music to help with pain management) have been very limited. Virtual reality is another modality with the potential to provide meaningful activity. Pilot testing shows virtual reality use among hospice patients living

TABLE 79.1 Guidelines for Assessing Pain With Older Adults With Cognitive Impairments

General Guidelines

1. Determine if Mini-Mental Status Examination scores are available or can be obtained. This would facilitate the determination of patient ability to provide valid self-report.
2. Always attempt self-report regardless of the level of cognitive functioning.
3. Baseline scores should be collected for each individual (ideally on a regular basis which would allow for the examination of unusual changes from the persons' typical pattern of scores).
4. Patient history and physical examination results should be taken into consideration.
5. If assessments are to be repeated over time, assessment conditions should be kept constant (e.g. use the same assessment tool, use the same assessor where possible and conduct pain assessment during similar situations).
6. Pain assessment results should be used to evaluate the efficacy of pain management interventions.
7. Knowledgeable informants (e.g. caregivers) should be asked about typical pain behaviors of the individual.
8. Other aspects of the pain experience should also be evaluated, including environmental factors, psychological functioning, and social environment.

Recommendations Specific to Self-Report Measures

1. Use of synonyms when asking about the pain experience (e.g. hurt, aching) will facilitate the self-report of some patients who have limitations in communicating verbally.
2. Self-report scales should be modified to account for any sensory deficits that occur with aging (e.g. poor vision, hearing difficulties).
3. Use self-report tools that have been found to be most valid among older adults (e.g. the Numeric Rating Scales, Verbal Rating Scales).
4. Use of horizontal visual analog scales should be avoided as some investigators have found unusually high numbers of unscorable responses among older adults.
5. Observational tools that have been shown to be reliable and valid for use in this population include the PACSLAC-II and PAINAD. Nonetheless, clinicians should always exercise caution when using these measures because they are relatively new, and research is continuing.
6. When assessing pain in acute-care settings, tools that primarily focus on evaluating change over time should be avoided.
7. Observational assessments during movement-based tasks would be more likely to lead to the identification of underlying pain problems than assessments during rest.
8. Some pain assessment tools, such as the PACSLAC scales, do not have specific cut-off scores because of recognition of tremendous individual differences among people with severe dementia. Instead, it is recommended that pain is assessed regularly (establishing baseline scores for each patient), with the clinician observing score changes over time.
9. Examination of pain assessment scores before and after the administration of analgesics is likely to facilitate pain assessment.
10. Some of the symptoms of delirium (seen frequently in LTC) overlap with certain behavioral manifestations of uncontrolled pain (e.g. behavioral disturbance). Clinicians assessing patients with delirium should be aware of this. On the positive side, delirium tends to be a transient state, and pain assessment, which can be repeated or conducted when the patient is not delirious, is more likely to lead to valid results. It is important to note also that pain can cause delirium, and clinicians should be astute to avoid missing pain problems among patients with delirium.
11. Observational pain assessment tools are screening instruments only and cannot be taken to represent definitive indicators of pain. Sometimes, they may suggest the presence of pain when pain is not present, and other times they may fail to identify pain.

Outcomes of Interest

In addition to improved scores on various assessment tools, evidence of more effective pain management can be observed in areas such as greater participation in activities, improved sleep, reduced behavioral disturbance, improved ability to ambulate, and improved social interactions.

Table Note: Many of these recommendations have been adapted from Hadjistavropoulos et al. (2007). Many of these recommendations also overlap with those of Herr et al. (2006) and Herr et al. (2019).
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with dementia was mostly safe and enjoyable in this population.[77] Nonetheless, the headset needed for virtual reality may be challenging to implement because many patients with advanced dementia may find it uncomfortable or be unwilling to use it.

In terms of psychological interventions, Cipher et al.[78] demonstrated that a multimodal intervention with LTC residents who had mild to moderate dementia was helpful with pain and mood management. The intervention involved the participation of caregivers/family members and behavioral interventions. More specifically, caregivers/family members assisted with rehabilitation (e.g. by facilitating patient cooperation) and social reinforcement. Participants benefited in terms of pain reduction, depression, and emotional distress as measured by validated tools that were at least partly reliant on caregiver/clinician input.

As far as older adults with moderate to severe dementia are concerned, we know that persistent pain often leads to mood deflation and depression in cognitively intact persons.[78] To the extent that this applies to people with dementia, psychological interventions designed to enhance mood management could help improve the quality of life of those who suffer from pain. Terri, Logsdon, Uomoto et al.[79] have shown that behavioral interventions (e.g. engagement in pleasant activities, caregiver involvement)

can improve mood in older individuals with dementia. Such interventions may help enhance the wellbeing of older adults with dementia who suffer from persistent pain.

Pharmacologic Pain Management

Consistent with a multimodal, collaborative approach to managing older adults with dementia and chronic pain, incorporating goals of care and expectations (from patient and caregiver) is a critical first step. The literature,[80] although not specific to patients with dementia, suggests that pain relief is one of the most commonly endorsed goals of older adults. Guidelines for the management of chronic pain recommend nonpharmacologic and behavioral interventions as first-line.[81] While there are limited studies in patients with dementia and pain, this population is particularly vulnerable to adverse events from medications, largely because of multimorbidity and polypharmacy.[82] Pharmacologic modalities for chronic pain in older adults with dementia are one component of the multimodal, interdisciplinary management of these complex conditions. Much of the summary below is derived from literature from younger adults as there is a paucity of randomized controlled trial (RCT) data on efficacy and safety, specifically in older adults with dementia.[83]

Thermal and Topical Therapies

While the etiologies for chronic pain in later life are broad, the most common and disabling are musculoskeletal pain (including osteoarthritis [OA] and chronic back pain). Recent guidelines from the American College of Rheumatology[84] (ACR) provide a conditional recommendation that thermal modalities, including trials of cold or warm compresses, applied to the painful sites (hand, knee, hip OA) may be beneficial. Caution must be used to avoid burning the skin with heating pads over long periods.

Topical medications for pain control are particularly appealing in older adult populations, given the safety profile because of limited systemic absorption. Currently available topical preparations are menthol, capsaicin, lidocaine, and diclofenac. The recent ACR guidelines do not recommend capsaicin for hand OA, although it has a conditional recommendation for knee OA. It would be important to ensure that patients avoid contact with the face/eyes since capsaicin is derived from hot peppers. Lidocaine, as a cream or patch, can be used for neuropathic pain. Since the patches require replacement at specific time intervals, this option is less ideal if the patient has dementia and is managing his or her medications. Perhaps the most commonly used topical agent is diclofenac, which is used mostly for knee and hand OA. A literature review[85] revealed that topical NSAIDs in older adults (age >60 years old) were nearly as effective and carried a lower risk of severe adverse events (gastrointestinal) compared to oral NSAIDs. While most RCT excluded older adults with renal impairment or who were anticoagulated, topical diclofenac has been used safely at a reduced frequency (twice/day instead of four times/day) in this population.

Acetaminophen

Acetaminophen (APAP) is often used as a first line analgesic for mild to moderate pain. In one systematic review[86] (including 137 studies with 33,243 participants, median age of 62 years), comparing APAP, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo, all interventions were significantly better than oral placebo for improving pain outcomes. While APAP had the lowest effect size (0.18) of the evaluated medications, its safety profile was also superior to oral nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). In a review of three RCT evaluating 140 patients with dementia, APAP was found to be well tolerated in doses up to 3 grams/day.[87] Review of medications (including those purchased over the counter) is important and should account for all sources of APAP. The long term (greater than three months) efficacy and safety of APAP in patients with dementia have not been proven.

Oral Non-steroidal Antiinflammatory Drugs

While potentially effective at treating pain and inflammation, the use of oral NSAIDs in older adults for long term use is discouraged because of known cardiovascular, gastrointestinal (GI), and renal toxicity.[88] Indomethacin may have a higher risk of adverse effects, including GI and renal effects.[87] Until additional research on the use of NSAIDs in older adults with dementia is conducted, the interdisciplinary team should weigh the risks and benefits of NSAID use and aim for the lowest effective dose for a brief duration. Patients taking NSAIDs should undergo regular monitoring of their renal and liver function.

Opioids

Opioids are not included in guidelines as first line management. If used, these medications are often trialed after other medication classes are not effective at improving pain or function. Known adverse effects in this population include falls, mental status changes, constipation, sedation, nausea, potential for increased agitation, respiratory depression, and sometimes death.[87] Tramadol, while included in the ACR guidelines, as conditionally recommended for hand, knee, and hip OA also has a concerning adverse effect profile and has not been evaluated specifically in patients with dementia. Oxycodone and morphine have been evaluated in patients with dementia and were found to reduce pain. However, the risk/benefit ratio must always be evaluated, taking individual risk factors into account. Additional research is needed as prior studies enrolled a small number of patients[89] and had a short duration (~ four weeks). Buprenorphine is a potent analgesic with mixed activity at the μ, κ, and δ receptors. Over 50% of subjects (all LTC patients with moderate to severe dementia and depression) who received buprenorphine in that study discontinued treatment because of adverse events (categorized as either neurologic or psychiatric).[90]

Adjuvant Therapies

There are very few trials that investigate the efficacy and safety of adjuvants such as anti-depressants, antiepileptic, or muscle relaxants in treating patients with pain and dementia. Many of these medications are listed on Beer's criteria as potentially inappropriate in older adults, based on a higher risk of adverse events, interaction with other medications, and impact on comorbidities. One trial evaluated a pragmatic approach to a stepwise protocol for treating pain in LTC patients with moderate to severe dementia and behavioral disturbances as compared to usual care (n = 352).[91] The protocol included an individualized approach to trialing APAP, morphine, buprenorphine, or pregabalin for eight weeks duration with a primary outcome of change in agitation. Of 12 patients who received pregabalin, 2 (16.7%) withdrew from the study because of somnolence, nausea, or drowsiness.

General Limitations

When older adults with dementia and pain are included in trials, this population is particularly prone to risks of both under- and over-reporting of adverse events. Existing trials are not designed to appropriately evaluate the cause and effect of medications on pain or other outcomes. Many questions remain to be answered regarding efficacy, safety, and improved outcomes that matter most in this population. Longitudinal and RCT designs will be integral to moving this field forward and improving outcomes for this vulnerable population.

Conclusions

There are challenges in assessing pain in people with limited ability to communicate because of dementia, but well validated observational approaches, focusing on pain behaviors, are available and are important supplements to clinical examinations and information obtained from knowledgeable informants. More research is needed on both pharmacologic and nonpharmacologic interventions, specifically focusing on people with dementia. Given the complexities involved in treating pain in this population, interdisciplinary collaborations involving physicians, psychologists, physical therapists, and other health professionals would be of the essence.[92]

Appendix A: Pain Assessment Checklist for Older Adults with Limited Ability to Communicate-II (PACSLAC-II)

Date of Assessment:Time:	Check If Present
Facial Expressions	
1. Grimacing	
2. Tighter face	
3. Pain expression	
4. Increased eye movement	
5. Wincing	
6. Opening mouth	
7. Creasing forehead	
8. Lowered eyebrows or frowning	
9. Raised cheeks, narrowing of the eyes or squinting	
10. Wrinkled nose and raised upper lip	
11. Eyes closing	
Verbalizations and Vocalizations	
12. Crying	
13. A specific sound for pain (e.g. 'ow,' 'ouch')	
14. Moaning and groaning	
15. Grunting	
16. Gasping or breathing loudly	
Body Movements	
17. Flinching or pulling away	
18. Thrashing	
19. Refusing to move	
20. Moving slow	
21. Guarding sore area	
22. Rubbing or holding sore area	
23. Limping	
24. Clenched fist	
25. Going into fetal position	
26. Stiff or rigid	
27. Shaking or trembling	
Changes in Interpersonal Interactions	
28. Not wanting to be touched	
29. Not allowing people near	
Changes in Activity Patterns or Routines	
30. Decreased activity	
Mental Status Changes	
31. Are there mental status changes that are because of pain and are not explained by another condition (e.g. delirium because of medication)?	
TOTAL SCORE (Add up checkmarks)	

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Key Points

- Pain is challenging to assess in older adults with moderate to severe dementia because of limitations in ability to communicate pain because of cognitive and linguistic impairments.
- While older adults with mild to moderate dementia may be able to report on their pain using unidimensional scales, validated systematic observational approaches such as the PACSLAC-II or the PAINAD are needed to monitor pain levels in those with moderate to advanced dementia.
- Consensus guidelines for assessing pain in people with dementia are available.
- Research on nonpharmacologic pain management interventions is limited but does suggest that physical therapy, exercise therapy, sensory stimulation, and various comfort modalities show promise.
- Pharmacologic pain management research specifically focusing on older adults with dementia has been limited, and clinicians often extrapolate from studies based on younger persons without dementia.
- The pharmacologic modalities should be chosen based on goals of therapy, as discussed with the older adult and caregiver, and also tailored and monitored according to other medications used and concurrent comorbidities managed.
- A multimodal interdisciplinary approach of a combination of nonpharmacologic and pharmacologic modalities for pain may be particularly appropriate in older adults with dementia and should be tailored and monitored for safety according to goals of therapy, and other medications used to managed comorbidities.

Suggested Readings

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Disparities in Pain Care: Descriptive Epidemiology-Potential for Primary Prevention

JANA M. MOSSEY

Background to this Chapter

This chapter is being written at an unprecedented time in the history of the United States. The coronavirus (SARS-CoV2) pandemic has swept across the country. COVID-19 case numbers, hospitalizations, and deaths show non-Hispanic Blacks, American Indians, and Hispanics to have been disproportionately affected.[1,2] The Centers for Disease Control (CDC) has reported age adjusted mortality rates for non-Hispanic Blacks and American Indians are over twice that of non-Hispanic Whites, and age adjusted hospitalization rates for Hispanic, and non-Hispanic Blacks are almost five times greater than that for non-Hispanic Whites.[3] These large disparities in COVID-19 mortality and hospitalization are attributed to the long term detrimental effects of systemic/structural racism,[4–6] manifest in persistent discrimination and unequal opportunity, poverty, segregated crowded residential neighborhoods, and current employment in "essential" low paying jobs that require the use of public transportation.[7–10]

On March 25, 2020, the horrifying death of George Floyd, an unarmed non-Hispanic Black male, was televised. Mr. Floyd's death has stimulated a widespread and continuing resurgence of and support for the "Black Lives Matter" movement.[11–13] These two events have made it virtually impossible for most individuals to continue to believe that "racism" in the United States ended in the 1960s or to deny that non-Hispanic Blacks, in particular, continue to be impacted by discriminatory racial biases. Currently, the difference between "not racism" and "antiracism" is being discussed widely, and actions necessary to be an "anti-racist" are being disseminated through news and social media.[14,15] Coincident with this, healthcare professionals are acknowledging the influence of systemic/structural racism on the healthcare system and, consequently, the health of disadvantaged minority populations.[16–19] In a recent issue of the Journal of the American Medical Association (JAMA), Hooper et al. wrote, "*The pandemic presents a window of opportunity for achieving greater equity in the healthcare of all vulnerable populations.*"[16] In mid-July, an editorial in the New England Journal of Medicine by Evans and his colleagues stated: "*Now, amid an acute public health crisis that is transforming medicine, perhaps we have an opportunity to reset our priorities to face this deeper, more chronic crisis as well.….Even if we can't change the social determinants of health for any individual patient in any given encounter, we can think more seriously about how they affect what the patient can and can't do, tailor the patient's care accordingly, and show that we are invested.*"[17] These sentiments suggest healthcare providers may be ready to accept the challenge of moving beyond a healthcare system constrained by the influences of systematic/structural racism to one in which health care is equitably delivered and universally accessible.

In addition to the above secular events, two recent developments provide additional impetus for specific change in pain management. Consequent to the opioid epidemic, the CDC[20] has issued restrictive guidelines that substantially limit opioid prescriptions for acute and chronic pain care. Practitioners and patients are faced with new challenges regarding which medication regimens and/or nonpharmacologic treatment approaches will work best.[21,22] The opportunities for doctor/patient decision making with regards to non-opioid treatment options can result in patient empowerment and increased treatment adherence. A second important change in pain management is the recognition that optimal care requires a multi-disciplinary group of pain practitioners (e.g. pain psychologists, physical therapists, and complementary medicine specialists) who join the physician and the patient in the planning and implementation of pain treatment plans.[23,24] With less reliance on opioid analgesics, this is a promising development. When fully operational, providers and patients will need to work creatively to ensure that patients who will benefit from important nonpharmacologic interventions will be able to access and pay for them.

Part I: Introduction

For most of the past 25 years, low back pain has been the number one cause of "years lived with disability" (YLD) worldwide.[25] As such, low back pain accounts for more disability burden across the globe and in the United States than any other disease or injury.[26] Acute and chronic pain are highly prevalent. Drawing on CDC data for 2016, Dalhamer et al.[27] indicate that 20.4% of the United States adult population (~50 million individuals) suffered from chronic pain. Total overall annual treatment costs associated with pain have been estimated to exceed 600 billion dollars.[28] Treatment costs represent only a small part of total pain costs. The physical and emotional suffering, loss in life quality, work

productivity, and creativity experienced by individuals in pain and that experienced by family and friends are major additional costs. Both the World Health Organization statement on health as a human right,[29] and the National Pain Strategy endorse the goals of equal access to health and health care for all individuals and reduction or prevention of the burden of pain across the life span.[30]

In 1993, Todd et al.[31] reported that Hispanics seen in the emergency department (ED) with a long bone fracture received inferior pain care compared to that received by non-Hispanic Whites. The Hispanics received no analgesic or a lower strength non-opioid analgesic, while non-Hispanic White patients received opioid analgesics. In 2000, Todd et al.[32] reported similar disparate care received by non-Hispanic Blacks treated for acute pain in the ED. Over the past 27 years, many research papers, review articles,[33–37] and government reports have documented racial/ethnic disparities in pain care,[38–40] and pain care providers and educators have been challenged to find solutions to the problem.[41,42] Despite their efforts, unequal pain care to minority groups continues as a pernicious and troubling aspect of contemporary pain management. This chapter addresses the questions: "Is the primary prevention of disparate pain care to minority groups a possibility?"; and "If thought to be possible, what can pain care practitioners do to diminish or prevent the delivery of unequal pain care?" To develop answers to these questions, Part I addresses the epidemiology of pain care disparities. An operational definition of disparate care with the selected process and outcome indicators is presented. The populations at risk of such care are identified, findings from research studies pertinent to the identified indicators are summarized, and the consequences of suboptimal pain care are discussed. Part II presents contributing causes of inadequate pain care. In Part III, the potential for the primary prevention of disparate pain care is addressed, and actions pain care practitioners may take to diminish or eliminate their contributions to disparate care and to ensure optimal pain care for ALL are identified.

Part I: Epidemiology of Disparities in Pain Care

Definition of Disparities and Indicators of "Suboptimal" Pain Care

The Oxford Dictionary defines the term *"disparities"* as "a difference especially one connected with unfair treatment."[43] While helpful, a clinical definition of "unequal or disparate treatment" is missing. From an epidemiologic perspective, an operational definition of unequal or suboptimal pain care is important. However, no comprehensive definition has been identified. Because of the privileged status of most non-Hispanic Whites, researchers have used the pain care received by them as a metric against which to compare that received by other racial, ethnic, or marginalized groups. Since most of the published studies preceded recommendations to restrict opioid prescribing, less frequent or lower dose administration of opioid analgesics was most often the study variable that indicated suboptimal or optimal care.[35,37] Selected process and outcome indicators of suboptimal pain care reported in the literature or deemed critical to evaluating pain care are presented in Table 80.1. As researchers, clinicians, and patients gain a greater understanding of the effective pain care strategies that supplement or replace those specific to a prescription of opioid analgesics, it will be important to identify new process and outcome indicators for both optimal and suboptimal pain.

TABLE 80.1 Selected Process and Outcome Indicators of Suboptimal Care for Acute and Chronic Pain

Indicators	Citation Numbers
Patient's pain level was not assessed by the treating provider	62–65,67,68,101
Provider's assessment of patient's pain level is lower than patient's self-report	70,73,74,87,88,
Provider failed to prescribe any analgesic to a patient with pain compared to a similar White patient treated for pain	63–65,75,76
Provider failed to prescribe opioid analgesic to patients with substantial pain compared to a similar White patient treated for pain	60,62–65, 77-87,91–95
Excessive time delay from emergency department (ED) arrival to administration of appropriate analgesic	104,105
At ED, hospital, primary care physician (PCP) office discharge, provider prescribed no opioid analgesic or an opioid analgesic of inadequate strength for the patient's pain level and disease status	66,84,88
At ED, hospital, PCP office discharge, provider required return visits for a patient prescribed an opioid analgesic at a shorter interval than for typical patients	96,97
Patient/provider visit is shorter than provider's average patient visit time	127
Provider diminished or dismissed patient's self-reported pain and discharged patient from ED or outpatient office without thorough evaluation	98,99,100
Acute pain patient seen in ED or surgery transitioned into post-surgical chronic pain	111–117
Acute or chronic pain patient developed post-traumatic stress disorder or post-traumatic stress syndrome following treatment	118,119
Acute or chronic pain patient developed misuse or abuse of prescribed narcotic analgesic	96,97

Indicators are drafted based on a single patient. Evidence of disparities in pain care exists if the rate of suboptimal pain delivered to race/ethnic or other marginalized groups exceeds the comparable rate of suboptimal pain delivered to the comparison group.

Population Groups at Risk of Disparities in Pain Care

Many contemporary scientists, this author included, view "race" as a socio-political construct instead of a complete biologic phenomena informed only by a group's genetic makeup.[44–46] The conclusion that "race" is predominantly contrived rather than entirely determined by genetics remains controversial given population based genome studies and the interest in the identification of gene disease markers.[47] While results of the Human Genome Project have shown that humans have 99.9% of their genetic material in common,[48,49] the differences remain unresolved between 1) the view that race is genetic and 2) the view that the effects of social and environmental exposures have contributed to the development of intergroup phenotypic differences such as skin color, hair texture, and eye color. Although no credible evidence supports the theory that non-Hispanic Whites represent a superior racial group and all other population groups are genetically

inferior, White Nationalists explicitly support this racist theory. Other non-Hispanic Whites may have implicit biases they are not consciously aware of that support the supremacy of non-Hispanic Whites. Beginning with the practice of slavery, the racist viewpoint has had a longstanding history in the United States. Currently, the population is hierarchically organized, with non-Hispanic Whites the privileged holders of wealth and power; non-Hispanic Blacks, Hispanics, and other groups are devalued and limited in their access to power, wealth, opportunity, and material goods.[44,50] Although considered arbitrary, the race/ethnic classification established by the United States Office of Management and Budget that includes[51] non-Hispanic Whites, non-Hispanic Blacks, Hispanics, American Indians or Alaska Natives, Asians, and Native Hawaiian or other Pacific Islander has become a principal classification variable used for the organization of Census Statistics and most health related research. It is used throughout this chapter. Following an informal scientific convention, non-Hispanic Whites are typically considered the "reference" or 'comparison" group. In addition to race/ethnicity, other population groups have been classified, some or all of the time, as "minority" or "marginalized." Such groups include American Indian/Native Alaskans, Asians, Native Hawaiian/other Pacific Islander, individuals who are poor, individuals with intellectual, physical, or emotional disabilities, older adults, women, persons who do not self-identify as heterosexual male or female, and those who ever have been incarcerated.[52,53] Collectively, these groups comprise the population at risk for disparate pain care.

Disparities in Pain Care: Summary of Recent Evidence

The substantive conclusions from previous research specific to the indicators listed in Table 80.1 have changed very little from the findings presented in earlier review papers published by Green et al.,[33] Anderson et al.,[36] Mossey,[34] and Meghani et al.[35] Consequently, updated findings reported in more recently published research papers are only very briefly summarized below.

Acute Pain Care: Emergency Department, Primary Care Settings

Acute pain is often treated in the ED, primary care outpatient offices or clinics, and the hospital pre- and post-surgery units. Typically, the treatment process includes 1) the identification of the patient's self-reported pain level; 2) the development of a clinical pain level assessment based on the provider's interpretation of the patient's self-reported pain and other relevant clinical information; and 3) selection and administration of an analgesic that is deemed safe for the patient and commensurate with the patient's reported pain level. Until the recent CDC guidelines in opioid prescribing for acute and chronic pain,[20] the prescription of an opioid analgesic has differentiated suboptimal pain care from optimal pain care. While some studies have reported no racial/ethnic disparities in analgesic prescribing,[54–57] the most consistent findings showed non-Hispanic Black and Hispanic pain patients, compared to non-Hispanic Whites, have received suboptimal pain care in the ED, outpatient offices, and the hospital.[58–62]

Recognized as a critical driver of the providers' analgesic prescribing, studies show self-reported pain levels of child and adult patients seen in the ED and other outpatient settings were not assessed as frequently for non-Hispanic Blacks and Hispanics as for non-Hispanic Whites. This disparity occurred during Emergency Medicine Service (EMS)[63–65] transit to the ED and after admission to the ED,[63,66,67] or attendance at primary care offices.[68] There is considerable evidence that when non-Hispanic Blacks and Hispanics self-report their pain level, their report is an underestimation of the pain they actually feel.[69,70] Researchers have speculated that such under-reporting may reflect the patients' internal pressures to maintain their self-image, cultural expectations, or fear that they will be perceived by healthcare providers as "complainers."[71,72] Strong evidence explaining their tendency to under-report pain is not available. Simultaneous to the recognition that non-Hispanic Black and Hispanic patients underestimate their pain, clinical and experimental studies report that many providers believe these patients exaggerate their pain.[73,74] As a result of the patients' and providers' misrepresentations, compared to non-Hispanic Whites, non-Hispanic Black, and Hispanic children and adults are more likely to receive no analgesic during EMS[63–65] transport to the ED and during an ED visit for a painful condition.[75,76] When analgesics are prescribed, non-Hispanic Black and Hispanic children,[62–65,77–81] and adult pain patients [60,82–86] seen in the ED consistently are less likely to be administered an opioid analgesic than non-Hispanic Whites. For example, in a study of the treatments and outcomes of children seen in the ED for a long bone fracture, non-Hispanic Blacks and Hispanics were more likely than non-Hispanic Whites to receive any analgesic [non-Hispanic Black adjusted odds ratio (aOR) 1.72 (95% confidence interval [CI] 1.51–1.95), Hispanics AOR 1.32 (1.16–1.51)]. However, they were less likely than non-Hispanic Whites to be prescribed an opioid analgesic [non-Hispanic Black AOR 0.86 (0.77–0.95) Hispanic AOR 0.86 (0.76–0.96)] or to achieve optimum pain reduction [non-Hispanic Black AOR 0.78 (0.67–0.90); Hispanic AOR 0.80 (0.67–0.95)].[80] Comparable to the experience of children, for adults with moderate to severe pain, the adjusted risk of receiving an opioid analgesic was 17% to 30% lower for non-Hispanic Blacks and Hispanics than for non-Hispanic Whites.[86]

Pre- and Post-Op and Postpartum Acute Pain Care to Ethnic/Racial Minorities

Recent studies indicate persistent ethnic/racial disparities in pre- and post-op pain care to children and adults. Compared to non-Hispanic White children, Hispanic, Pacific Islander, or Asian children were at lower odds [AOR 0.87 (95% CI 0.74–0,97); AOR 0.53 (0.33–0.84); AOR 0.83 CI 0.70–0.97], respectively, of receiving important post-op non-opioid analgesics.[87] Baldreldin et al. reported that while Hispanic and non-Hispanic Black postpartum women reported higher pain scores than non-Hispanic Whites, they received significantly fewer inpatient MMEs and were less likely to receive a prescription for an opioid analgesic [Hispanic AOR 0.80 (95% CI 0.67–0.96), non-Hispanic Blacks AOR 0.78 (0.62–0.98)].[88]

Chronic Non-cancer Pain

Chronic pain is one of the most difficult pain diagnoses for the provider and patient to manage. Suffering can be extreme, and patients often feel desperate for relief. Studies indicate the prevalence of chronic pain is lower in non-Hispanic Whites; the intensity of the pain and the level of pain interference is greater among non-Hispanic Blacks and Hispanics.[89] Recently divided into high impact chronic pain (HICP), pain with activity limitations, and low impact chronic pain (CPWL), pain without limitations,

Dahlhamer et al. reported 8.0% of the adult population in 2016 suffered from HICP, and 20.4% experienced CPWL.[90] Studies show non-Hispanic Blacks and Hispanics continue to receive suboptimal chronic pain care more frequently than non-Hispanic Whites.[82,91–95] In outpatient settings, studies indicate the percentage of non-Hispanic Blacks and Hispanics receiving opioid analgesics was smaller than for non-Hispanic Whites. Non-Hispanic Blacks were prescribed fewer opioid pills and required to return for urine testing more frequently than non-Hispanic Whites. Prescription of fewer drugs and more frequent monitoring for opioid misuse suggest pain providers are more likely to distrust non-Hispanic Black patients than non-Hispanic White patients, even though there is no evidence that non-Hispanic Blacks are more likely to misuse or divert prescribed medications for chronic pain.[96,97]

Other non-minority groups, including females and older adults, experience disparate chronic pain care. Compared to males, physicians tend to withhold giving females opioid analgesics, female pain levels are dismissed more frequently, and women are referred to pain specialists less often than males.[98,99] The experience of women whose physician diminishes their pain is particularly difficult and, very likely, demeaning to the patient. Comments of a Black female quoted in a qualitative study indicated: *"You could just tell that he just didn't believe me that I was in as much pain as I was. He was just very unsympathetic. He would literally walk away while I was in the middle of a sentence."*[100]

Ethnic/Racial Disparities in Cancer Pain Care

Non-Hispanic Blacks are at increased risk of presenting for medical care with advanced cancer than non-Hispanic Whites. They have poorer outcomes for many cancer diagnoses and are less likely than non-Hispanic Whites to receive advanced cancer treatments or, when transferred to a nursing home, to have their pain level assessed.[101] In a study of Medicaid cancer patients, Halpern et al. reported non-Hispanic Blacks and Hispanics were half as likely as non-Hispanic Whites to receive interventional pain treatments for breast cancer.[102] In a study of racial disparities in the treatment of metastatic spine disease, non-Hispanic Blacks were less likely than non-Hispanic Whites to undergo surgery; they had longer hospital lengths of stay and were more likely to experience a complication.[103]

Consequences/Outcomes of Suboptimal Pain Care

The primary objectives of acute pain treatment are to alleviate the patients' immediate suffering and to minimize the activation of pain related neurophysiologic and/or psychological processes that may lead to irreversible negative outcomes, central nervous system changes, or progression to chronic pain. Non-Hispanic Black and Hispanic patients are at increased risk of experiencing longer periods of untreated acute pain; they experience longer premedication waits in the ED,[104,105] and fewer appropriate medication prescriptions at discharge than non-Hispanic Whites.[106,107] Prolonged acute pain from long waits in the ED before receiving an effective analgesic can evoke anxiety, fear, panic, desperation, or helplessness. Other feelings that can occur include a personal sense of inadequacy, worthlessness, or invisibility. Discharge from the ED or hospital without a prescription for analgesia of sufficient strength can prolong emotional and physical suffering and increase anger and distrust.

The long-term effects of inadequately anesthetized immunization experiences of infants highlight their vulnerability to "intense pain" and the likelihood of developing negative memories about pain. Taddio et al.[108] noted that "fear of needles" developed during infancy can persist for many years and jeopardize future preventive health care. They reported that 90% of toddlers and 45% of primary school children continued to experience extreme distress during later childhood immunizations. Indicative of the lifetime implications of early unprotected immunizations or inadequately treated pain, McLennan and Rogers observed that 16% of adults still showed signs of needle phobia.[109] The limited number of longitudinal studies that track the consequences of early childhood pain exposure through adulthood makes it difficult to fully understand its impact throughout the life course.

Transition From Acute to Chronic Pain and Post Surgery Chronic Pain

The transition to chronic pain from an acute pain episode treated in the ED or an acute surgery related pain is a serious negative, disabling outcome. Researchers have observed that as many as 43% of adults seen in the ED for acute pain report persistent pain three months after the ED visit. The predictors of not fully recovering included baseline anger, sleep disturbances, low Socioeconomic Status (SES), and post traumatc stress disorder (PTSD) symptoms.[110] Post-surgical chronic pain (PSCP), defined as pain occurring at the surgery site and lasting longer than the expected healing time, is a more critical and disabling outcome of acute pain. As Glare et al. note, *"Neuropathic descriptors [of PSCP] such as hyperalgesia (heightened sensitivity to painful stimuli), dysaesthesia (an unpleasant, abnormal sense of touch), and allodynia (sensitivity to normally non-painful, often repetitive, stimulation) are frequently used."*[111] PSCP is associated with comorbid symptoms including depression, anxiety, and sleep disturbance.[112]

While the predictors of PSCP have not been fully identified, observed risk factors include severe, difficult to treat post-surgical pain, female gender, fear of surgery, perceived self-helplessness, and pain catastrophizing.[112,113] The importance of race or ethnicity as a predictor of PSCP has not yet been fully clarified.[112] Gungor et al.[114] report that non-Hispanic Blacks were at substantially higher risk for persistent post-surgical pain (PPP) following total knee arthroplasty than non-Hispanic Whites. While PPP is distinct from PSCP, they share some risk factors, including intense pre/post-surgical pain, psychological symptoms, and prolonged surgical site pain, depressive symptoms, and pain catastrophizing.[111,114] It is reasonable to conclude that, like PPP, non-Hispanic Blacks could be at increased risk for PSCP. Reported incidence rates for PSCP in adults range from 10% to over 50%,[111,113] and in children 10% to over 20%.[115,116]

Positive associations between PPP and PTSD are suggestive, but the research findings are less clear. Based on their literature review, Fishbain et al.[117] concluded that the association between chronic pain and PTSD differed according to the type of pain and the population being studied. Ravn et al. reviewed the temporal associations between post-traumatic pain and post-traumatic stress. They concluded that further study was needed to clarify the nature of these relationships.[118] The evidence of serious acute pain leading to Post Traumatic Stress Symptoms (PTSS) in children and adolescents has also been studied. After a traumatic injury about 20% of children develop PTSS, and many may re-experience the traumatic event or manifest hyperarousal, dissociation, and mood or cognitive changes.[119]

Few studies of postoperative pain trajectories have included race/ethnicity as an independent variable. Suboptimal pain care provided to minority populations increases the occurrence of

undertreated pain. As posttreatment pain is a risk factor for transition from acute to chronic pain, it is reasonable to suspect that non-Hispanic Blacks and Hispanics, compared to non-Hispanic Whites, will disproportionately experience more negative complications such as PSCP and PTSD.

Part II: Factors Contributing to the Occurrence of Disparities in Pain Care

No one factor accounts for all suboptimal pain care received by disadvantaged groups. Recently, epidemiologists, social scientists, and clinicians have recognized that systemic/structural racism is largely responsible for the designation of a population group as inferior or unequal and the creation of a healthcare system where systematic suboptimal pain care is possible.[44,120,121] A thorough presentation of the background and historical trajectory of systematic racism is beyond the scope of this chapter. Instead, important aspects of systemic/structural racism are briefly summarized here. More thorough resources pertinent to racism are identified at the end of the chapter. According to Jones,[122] there are three levels of racism: "*institutionalized, personally mediated* [explicit and implicit racism]*, and internalized* [racism]."[122] Institutionalized racism is also referred to as systemic or structural racism; the term systemic racism will be used throughout the remainder of the chapter. These levels of racism and the contributions of each to disparities in pain care are addressed below.

Societal Issues: Systemic Racism

Systemic racism has had an extensive and persistent influence on the United States social and political systems and the historical devaluation of specific groups. Jones describes systemic racism as: "*differential access to the goods, services, and opportunities of society by race…* [that]*…manifests itself in material conditions and access to power. With regard to material conditions, examples include differential access to quality education…appropriate medical facilities, and a clean environment.*"[122] Bailey et al. further define systemic racism as "*the totality of ways in which societies foster discrimination, via mutually reinforcing systems (e.g. in housing, education, employment, earnings, healthcare, criminal justice etc.) that in turn reinforce discriminatory beliefs, values, and distributions of resources.*"[44] Since the country's beginning, non-Hispanic Whites have maintained a position of power and privilege. However, non-Hispanic Blacks descendent from slaves of African origin, American Indians, and Alaska Natives actively have been demeaned, diminished as lesser, and denied equal access to opportunities including wealth, education, and health care. Their lives have been diminished, first, by the brutality of being owned slaves and, more recently, by exclusion, prejudice, and discrimination.

Systemic Racism-Contributions of the Healthcare System in the United States

Consistent with systemic racism, the United States health care reflects non-inclusive policies that hinder equitable and equal access for all citizens.[18,123] For-profit, insurance financed access to most preventive healthcare and medical services depends on an individual's eligibility for Medicare or their ability to purchase health insurance privately or through their employer. Government programs such as Medicaid may support health care for the poorest individuals, but even with changes made under the Affordable Care Act,[124] many citizens have no health insurance or are under-insured. In 2019, 7.4% of non-Hispanic Whites were uninsured compared to 27.0% of Hispanics and 13.6% of non-Hispanic Blacks.[125]

Feelings of shame for inability to pay, fear of being turned away, or worry and anxiety because of the pressures of receiving a large medical bill result in the tendency of uninsured or under-insured individuals to delay seeking medical care. When finally seeking medical attention, their health problems, including painful conditions, are likely to be more advanced and more challenging to treat. Inability to pay for prescribed medications, physical therapy, or mental health services can result in prolonged suffering and being labeled as non-adherent. Because physicians have indicated that they have difficulty trusting patients who are non-adherent, the pain care patients' who do not adhere to prescribed treatments because of inability to pay are doubly compromised. The patient does not benefit, and the provider/patient relationship is compromised.[126]

A second issue reflective of systemic racism stems from policies inherent in the United States health service payment system. Reimbursement for delivered health services is essential to the financial stability of individual providers, healthcare agencies, and insurance companies. Inevitably, some uninsured patients who are unable to pay for health services do receive medical care. To compensate for this, insurance companies may lower reimbursement amounts paid to providers and healthcare facilities. As a consequence, private healthcare providers may be forced to see more patients each day. This inevitably shortens the time a provider has to spend with each patient. This can be a special problem for non-Hispanic Blacks and Hispanics as their visit time with providers often is already shorter than that for non-Hispanic Whites.[127] Financially challenged hospital systems, including those housing an ED, may have to function with fewer professional staff than optimal. Under this scenario, all pain care providers are likely to have short patient contact time, and they become at risk of experiencing work overload. Under such circumstances, providers are at increased likelihood of making racially biased patient treatment decisions.[128] Financial constraints may also diminish the ability to hire the number of competent translators needed to assist with patients whose ability to speak English is limited. When needed, the absence of such services decreases the likelihood that optimal pain care can be delivered.

Systemic Racism-Segregated Residential Neighborhoods

As a result of systemic racism, residential segregation exists in many cities and rural towns in the United States.[129,130] Residentially segregated neighborhoods characteristically are homogenous and under-resourced with a high proportion of low income, disadvantaged families and old, rundown housing stock. A high proportion of the neighborhood residents are likely to be uninsured or under-insured.[131,132] Typically, the neighborhoods are not attractive to physicians who could establish a primary care practice office. To address the absence of neighborhood primary care offices, the local health department may establish a primary care clinic in the neighborhood with services charged on a sliding scale. The United States trained physicians often are not interested in working in these "public" clinics. As a result, International Medical Graduates (IMG) are over-represented in their medical staff.[133] As noted by Meghani et al.,[35] IMG practitioners may not have important training in cultural competency. Even when an IMG provider is fluent in English, a regional accent may be challenging to patients. Pharmacies are particularly important for those who experience pain. In their study of pharmacy availability in selected geographic

sections of Michigan, Green and her colleagues[134] reported that individuals living in residentially segregated neighborhoods were at a substantial disadvantage in their ability to obtaining pain medications because of the unavailability of pharmacies or limitations on the medications stocked by the pharmacist.

Provider Contributions to Disparities in Pain Care

Limited Education

In their seminal paper, Todd et al.[31] suggested that lack of cultural competence might have accounted for the observed lower physician opioid prescribing to Hispanic ED patients than non-Hispanic Whites. Other investigators have suggested disparate pain care may result from inadequate provider education regarding all aspects of pain care, including symptoms and diagnoses of pain conditions, treatment approaches including those that are pharmaceutical and nonpharmaceutical, approaches to address patient non-adherence, financial inability to pay for prescribed treatment modalities, prevention, and management of opioid misuse. This concern is particularly relevant given the extensive reliance on primary care physicians for a large proportion of acute and chronic pain care.[135–137] Matthias et al. highlight the difficulties primary care physicians have encountered when working with hard-to-treat chronic care patients. They have used words such as "frustrating," "ungratifying," and "overwhelming" to describe their experiences.[138] Additional pain management training would increase provider competence. As noted earlier, IMG may also have critical limitations in their education, especially regarding formal training in cultural competence.[35]

False Beliefs Held by Physicians and Other Healthcare Providers

In their provocative paper, Hoffman et al. suggest that centuries old negative beliefs such as "non-Hispanic Blacks are insensitive to pain because their skin is thick," that had originally been promoted in an attempt to justify the physical abuse of slaves still exists as either explicit or implicit biases.[139] While Hoffman suggests beliefs originated in the times of slavery, Hogarth has presented compelling and disturbing evidence that, over the past centuries, physician scientists have contributed to the racist interpretation of non-Hispanic Blacks' physical attributes.[140] Although there is no evidence to support the negative characterizations, Hoffman and her colleagues have suggested they represent persistent "false beliefs" held by some health professionals that contribute to racial disparities in pain care.[139] A list of selected contemporary "false beliefs" about non-Hispanic Blacks is presented in Table 80.2. Research has shown that medical students and residents have endorsed, as true, some of the "false beliefs." In experimental studies, researchers also have found that the more "false beliefs" about non-Hispanic Blacks that were endorsed by a study participant, the more likely the respondent recommended lower dose analgesics for non-Hispanic Blacks than for non-Hispanic Whites.[139] As discussed in the next section, many providers are not consciously aware of holding "false beliefs." Such unconscious biases can influence behaviors and clinical decisions. For example, the "false belief" that non-Hispanic Blacks are more likely than non-Hispanic Whites to misuse or become addicted to prescribed narcotics is likely to have contributed to the disproportionate withholding of prescriptions for opioid analgesics from non-Hispanic Blacks at discharge from the ED, private doctors' offices, and the hospital.[106,107]

TABLE 80.2 Selected 'False Beliefs' About non-Hispanic Blacks that Have Persisted into the Twenty-first Century and Continue To Be Believed by Individuals Including Health Professionals

Selected "false belief"
Blacks are impervious to pain
Blacks lack intelligence
Blacks have weak lungs that could be strengthened through hard work
Blacks have blood that coagulates more quickly than whites*
Blacks' nerve endings are less sensitive than Whites'*
Blacks age more slowly than Whites*
Blacks' skin is thicker than Whites'*
Black males are violent
Black women are dominant and lazy
Black males are criminals
Blacks are genetically flawed
Blacks do not follow doctor's orders
Blacks do not take medications as prescribed
Blacks are more likely than Whites to abuse opioid analgesics
Blacks are superior athletes

*'False Beliefs' included in Table 80.1: Hoffman, et al.[139]

Personally, Mediated Racism: Provider Explicit and Implicit Racial Biases

Explicit biases refer to attitudes and beliefs (e.g. stereotypes) that are known to an individual. While individuals may be reticent to reveal explicit biases that are negative, they are open to self-report. As noted above, at an individual level, the "false beliefs" shown in Table 80.2 may represent an explicit or implicit bias. Implicit biases are unconscious and outside of the individual's awareness. They are extremely difficult to identify, even if the individual strives to do so. Once identified, considerable effort is required to manage or eliminate them. Of substantial importance to pain care providers, implicit biases represent an unconscious intrusion into the provider's ability to exhibit genuine empathy, to clearly hear what the patient says, to objectively observe and evaluate the patient, to develop an understanding of what the patient is feeling, and to develop a treatment plan with the patient that meets the patients' clinical needs and expectations.[139,141,142] It is important to acknowledge that the occurrence of implicit biases experienced by pain providers is equivalent to that observed in general populations.[143] As observed in other populations, it is possible that a pain practitioner might publicly support human rights, social justice, and equal access to and receipt of optimal pain care for all yet simultaneously harbor strong unconscious negative racial biases toward minority patients. Consistent with the above, there is substantial evidence showing that implicit biases can negatively affect aspects of the provider/patient relationship and lead to poorer patient outcomes.[141,142] One explanation for the apparent inconsistency between one's conscious assertions and held implicit biases draws on a model of cognitive processing known as "dual-system models" in which social cognitions are processed

by two interconnected mental systems that are thought to meet different cognitive needs and to reside in separate memory systems.[144–146] Social scientists have developed methods to indirectly measure implicit biases using the validated Implicit Association Test.[147] Of interest, researchers have observed weak correlations between an individual's explicit and implicit biases irrespective of race.[148] From the perspective of disparate pain care, results from experimental studies of hypothetical vignettes or virtual patients show the implicit biases of both non-Hispanic Whites and non-Hispanic Blacks are reflected in their preference for non-Hispanic White patients.[149]

Patient Characteristics That Contribute to Disparities in Their Care

There is emerging evidence that differences exist between non-Hispanic Blacks and non-Hispanic Whites in terms of neurophysiologic and biochemical processing of painful stimuli and neurochemical metabolism of opioid analgesics.[150–152] Experimental studies have shown non-Hispanic Blacks and Hispanics, compared to non-Hispanic Whites, to be more sensitive to painful stimuli, to feel pain as a more unpleasant sensation, and to have lower pain tolerance.[153–155] Studies to detect pain from changes in facial expression have found that non-Hispanic White study participants had much greater difficulty distinguishing painful from non-painful expressions when looking at non-Hispanic Black faces than when looking at those of non-Hispanic White individuals.[156] In real life, non-Hispanic Whites and non-Hispanic Blacks differ in their experiences of chronic pain. Non-Hispanic Blacks feel pain more intensely than non-Hispanic Whites; they develop comorbid depression more frequently, experience greater disability and activity limitations, more frequently personally blame themselves for pain, especially when the pain is chronic, utilize more passive, less successful, coping strategies such as prayer and pain catastrophizing, and have greater concern over the addictive properties of opioid analgesics.[157,158] Similar to Hispanics, they are likely to under-report their actual pain level. Within effective provider/patient relationships, these racial and ethnic differences should not increase the risk of suboptimal pain care because providers could have learned about such differences from conversations with their patients or from the existing research papers and review articles that address racial/ethnic pain care disparities.[33–37]

Although not well studied, some non-Hispanic Black and Hispanic attitudes and behaviors could increase their risk of receipt of suboptimal care. Jones has identified "internalized racism" as one category of systemic racism.[122(P1212)] Individuals of disadvantaged groups are at risk of believing the racist insults and negative characterizations that they hear. To the extent that this occurs, non-Hispanic Blacks and Hispanics may actually self-identify as inferior, genetically impaired, and worthless. Individuals with such feelings are likely to be reluctant to volunteer information to providers irrespective of whether they fully trust them. Out of feeling inadequate, they may be unwilling to be clear about their ability to afford prescribed medications, physical therapy, and/or psychological services. Their reticence to speak freely about their health insurance or job requirements may result in non-adherence to prescribed treatments. Non-adherence has special significance since physicians have indicated they have difficulty in trusting patients who do not follow their treatment instructions.[100]

Mistrust and Miscommunication Between Provider and Patient

Pain, whether acute or chronic, remains an individual experience identified in clinic settings by self-report. The subjective nature of pain poses an immediate challenge to a treating provider, especially one whose implicit biases may evoke distrust in the patient. Even if never spoken, the question, "Is the patient's pain report accurate?" may be raised. Because provider biases often lead to the diminution or dismissal of pain reported by racial/ethnic minorities, women, and older adults, their treatment plans frequently may not meet the patients' needs. Such provider behaviors can be interpreted by the patient as: "I do not trust you" or "I do not respect you." Acute and chronic pain patients have indicated they can feel disrespected, devalued, and unheard. Chronic pain patients interviewed during several qualitative studies described experiences with their pain provider using words like demeaning, traumatic, accusing. They indicated providers appeared uncaring, disinterested, disbelieving, and dismissive.[159–161]

Loss of trust in one's healthcare provider can have serious repercussions. In her recent memoir, *Becoming*, Michele Obama highlights the distrust non-Hispanic Blacks, irrespective of their economic status, can have toward physicians. She attributes her father's long delay in seeking medical care for symptoms of lung cancer to *"his long-held view that doctors were untrustworthy."*[162]

Mutual distrust between members of a patient/provider dyad increases the probability of miscommunication. It prevents the development of the positive therapeutic relationship that many consider necessary to the provider's and patient's abilities to jointly develop an appropriate care plan the patient is willing and able to adhere to.[163,164] In her compelling article on trust and race in American medicine, Sullivan emphasizes that, in situations where trust between the patient and physician has been broken or has never been established, the physician or other pain practitioner is the party responsible for establishing the conditions under which the patient will feel safe and willing to consider trusting their pain provider.[165] According to Sullivan, *"the practical questions are how patients can know that a physician is trustworthy and how physicians can convey their competence and caring appropriately."*[165] When asked which provider characteristics evoke trust, patients have indicated 1) technical competence (necessary but not sufficient) and 2) interpersonal competence (ability to communicate, taking time to talk with the patient, non-judgmental listener, showing caring); empathy; honesty; willingness to include patient in clinical decision making. Sullivan has added a third characteristic, "comprehension."[165] She describes "comprehension" as the willingness and ability to comprehend and acknowledge the larger context within which the individual lives and to understand where the patient is coming from and what is driving his or her decisions. Sullivan and others who have addressed trust and its significance for the establishment of effective provider/patient relationships recognize the potentially disruptive effects of implicit provider biases on their abilities to establish safe environments for patients who distrust providers and the healthcare system in general.[165]

PART III: Potential for the Primary Prevention of Disparities in Pain Care

Two questions were posed in Part I: "Is the primary prevention of disparate pain care to minority groups a possibility?" and "If thought to be possible, what can pain care practitioners do to diminish or

prevent the delivery of unequal pain care?" The term "primary prevention" refers to targeted actions to avoid negative health effects/outcomes.[166] Primary prevention may be as relatively straightforward as immunization against a disease or like suboptimal pain care to disadvantaged groups. It may be more complicated and require many targeted actions. In Part II, the factors that contribute to the occurrence and persistence of disparate pain care were identified as societal, legal, and health system consequences of structural racism, the continued existence of false beliefs regarding non-Hispanic Blacks, Hispanics, and other minority groups, limits in physician education, provider explicit and implicit biases, patient characteristics, and mutual patient/provider distrust. While some of these factors are complex, have long histories, would require enormous changes in the current societal allocation of privilege and power/disadvantage and oppression, they are not immutable. Theoretically, the primary prevention of disparate pain care to minority groups should be possible. However, it is naïve to suggest that pain care providers alone can achieve this goal. The challenge to those involved in pain management is to identify the actions that are uniquely under their control, to diligently and passionately address them head on, and to persist until disparities in pain care no longer exist, and, simultaneously, to direct efforts to eliminate systemic racism beliefs, policies, and laws from the healthcare system organization and delivery of care. The following identifies positive actions designed to diminish false provider beliefs, behaviors, and explicit and implicit biases that can increase pain care disparities. The success of the actions to be taken depends on understanding and accepting:

1. Pain care providers and educators must own their explicit and implicit biases and racist beliefs,
2. While taking responsibility, they should not feel personally culpable. During a televised "Town Hall Meeting," non-Hispanic Black leaders discussed systemic racism. Dr. Paula Johnson, President of Wellesley College, stated: *"And the absolute incorrect way to take this is to take it personally, because if you personalize it, then you become defensive. Of course, you are part of it. What we should say is [that] we are part of the United States of America, and therefore, of course, there is structural racism in our institutions,"*[167]
3. Pain care providers are responsible for correcting and eliminating their contributions to racial/ethnic and other minority group disparities in pain care. In her work on patient and provider trust, Sullivan emphasizes: *"In the work to resolve mistrust, the onus surely cannot lie with the potential trustee(that is, the patient) to reevaluate their understanding of the situation….To require individuals from a group that has historically been the subject of exploitation and discrimination to resolve the issue of mistrust in American medicine is to further burden them, exacerbating injustice,"*[165] and
4. Any work to prevent disparities in pain care will require constant attention and over-time repetition of discussions, skill training, seminars, and other activities until changed attitudes and behaviors are fully integrated.[168,169] Without continuous attention and refresher sessions, immediate changes are likely to dissipate and diminish.

Actions to be Taken by Individual Pain Care Providers

- Read the existing review articles and research papers that address disparities in pain medicine to become an expert in positive and negative or dysfunctional provider beliefs and behaviors. Identify personal positive and negative beliefs and behaviors. Develop and initiate a step-by-step plan to reduce negative or false beliefs and dysfunctional behaviors and reinforce positive ones.
- Talk with patients and colleagues to identify the meanings of pain and its expression among non-Hispanic Black, Hispanic, and other disadvantaged groups. Study the important cultural histories and health related norms held by Non-Hispanic Blacks and Hispanic individuals and other minority groups such as Asian individuals and LGBTQ (Lesbian, Gay, Bisexual, Transgender, Questioning) individuals.
- Learn about the history of racism, its past and contemporary impact on non-Hispanic Black individuals, and the role of non-Hispanic Whites in its origins and persistence.
- Engage with experts, colleagues, friends and read current materials authored by non-Hispanic Blacks to understand what it means to be an anti-racist. Become an anti-racist.

It is expected that the above actions would reflect honest self-assessments, persistent efforts, and active engagement with peers, experts, and individuals from many diverse population groups. It is not expected that an individual's implicit biases will have been fully identified and addressed. To increase the likelihood of identifying and managing implicit biases, structured, multi-session educational programs are recommended.

Actions to Develop and/or Refine Structured Multi-Session Educational Programs

While promising educational approaches to develop 1) cultural competence for healthcare providers or 2) recognition, acknowledge, and management of implicit provider biases exist, no educational programs for healthcare personnel with demonstrated effectiveness in terms of provider growth, temporal stability of desired attitudinal and behavioral outcomes, translation into measurable behavioral changes, and appropriately documented improvements in patient care outcomes have been identified for use within teaching institutions or clinical practices. A comprehensive review of the literature pertinent to existing educational or systematic reviews pertinent to programs to improve cultural competence or identification of implicit biases is beyond the scope of this chapter. However, the following provides some information relative to educational programs pertinent to cultural competence and addressing implicit bias.

Educational Programs to Develop Cultural Competence

It is widely recognized that healthcare providers should have knowledge regarding the cultural customs and norms of the patients to whom they provide health services.[170–171] Programs to increase the cultural competence of healthcare providers have been developed by individual institutions and delivered for several decades to most health profession disciplines. Although initiated with positive intentions, the authors' conclusions of a 2014 Cochrane systematic review on cultural competency programs were discouraging. While they noted findings *"showed some support for cultural competence education for health professionals. These findings are tentative…the quality of the evidence was low."*[171] The findings from several more recent systematic reviews have provided equally sobering conclusions.[172,173]

Educational Programs for Addressing Implicit Bias

To strengthen abilities to personally establish conditions under which pain patients who distrust providers could experience enough personal safety to enter into a trusting provider/patient

relationship, engagement in structured exercises designed for providers to recognize, acknowledge, and manage their implicit biases are crucial. Because implicit biases are often antithetical to the individual's self-perception, substantial resistance to self-disclosure is almost always present even if the individual intellectually agrees that he or she could have such biases. Several promising theoretically driven approaches ranging from a Mindfulness[174] approach to Translational Learning Theory[175] have been proposed as the basis of programs to identify and reduce implicit bias in healthcare providers. Further developmental and evaluative research is needed before any one educational program can be solidified. Until programs shown to meet the above education program criteria become available, pain practitioners are advised to read and discuss with colleagues written materials that focus on the presence and influence of implicit bias on provider behaviors and patient outcomes.

Actions to be Undertaken in Conjunction With Professional Organizations of Pain Providers

- Support the development and evaluation of the educational programs through which providers can:
  - 1) strengthen their ability to be "caring" practitioners, and 2) recognize, acknowledge, and manage the implicit biases that may negatively influence their ability to deliver optimum pain care to all individuals.
  - Establish methods and procedures to implement continuous evaluation of pain treatment services for acute and chronic pain to ensure that suboptimal care is not being delivered. If suboptimal pain care is observed, immediate corrective actions with providers and site personnel would be implemented.
  - Refine pain care process and outcome indicators such as those identified in Table 80.1 to assess optimal or suboptimal pain care in which administration of opioid analgesics is not a primary treatment approach.
  - Advocate for health system reforms that guarantee all individuals residing in the United States have access to equitable, quality health care irrespective of income level.
  - Partner with other medical and public health personnel and professional organizations to end systemic racism in every aspect of medicine and public health and in systems of education, housing, employment, and social and legal justice.

Conclusions

This chapter began with a 'Background' statement that identified the current socio-political context pertinent to the delivery of pain care. The inclusion of a description of the current status of disparate pain care provides the reader important content information. It has been instructive, though regrettable, to recognize that the research findings suggest that, in over 25 years, only modest progress has been made toward the reduction or elimination of disparate pain care. The significance of the chapter lies in a more thorough explanation of factors that contribute to discrepant pain care, the identification of some steps to increase the likelihood that disparate pain care could be prevented, and the specification of several requirements for healthcare providers who accept the challenges of moving from delivery of disparate pain care to delivery of uniformly equal quality pain care.

The over-arching conclusion is that, with persistent effort, the primary prevention of disparate pain care can be achieved. From a societal perspective, all forms of racism must be eliminated. To do so will require the efforts of all pain care providers as well as many others. From the perspective of pain care providers, the most critical but difficult undertaking is the acceptance by providers that they are responsible for establishing the conditions under which pain patients will feel free to trust them. The presence of promising educational programs to increase sustained provider cultural competence and enable providers to identify and manage implicit biases that interfere with patient trust is encouraging. Further development and evaluative research of relevant education programs is a high priority. To further guard against disparate pain care, research is needed to develop the continuous quality of care monitoring within both acute and chronic care settings. While the elimination of disparities in pain care is a challenge, it is a challenge worthy of addressing.

Key Points

- Chronic pain remains the leading cause of Years Lived With Disabilities worldwide and in the United States.
- Despite attempts to diminish disparities in the pain care to racial/ethnic and other minority groups, women, and older adults, suboptimal pain care to such groups persists.
- The unprecedented time in the United States because of the COVID-19 pandemic and the increased recognition and support for the Black Lives Matter Movement provides a unique opportunity to recognize and make systemic changes that could diminish or eliminate disparities in pain care.
- Systemic racism characterized by differential access to power, wealth, goods, and services has targeted non-Hispanic Blacks, Hispanics, and other minority groups. Non-Hispanic Whites have maintained a position of power.
- Systemic racism perspectives have influenced almost all institutions, including health care, education, housing, neighborhood composition, and criminal justice.
- Provider implicit biases, unconscious, typically negative attitudes and beliefs about minority groups, can affect clinical decisions and add to disparate pain care.
- Healthcare providers are responsible for establishing the conditions in which pain patients will feel safe and able to participate in a clinically effective doctor/patient relationship.
- Primary prevention of disparities in pain care is possible. To achieve this, healthcare providers will be challenged to address their part in disparate care, to ensure patients can trust them, and to insist that the healthcare system make anti-racist changes.

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81

Pain Management in the Critically Ill Patient

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Introduction

Pain in the critically ill has been historically poorly understood. Only recently has attention and investigation turned toward the issues of pain assessment and treatment in this patient population. The prevalence of poorly treated pain in the critically ill is considerable and greater than commonly believed among health care physicians. This chapter examines some salient issues as well as the modern, pertinent literature detailing barriers to assessing and treating pain in a critical care setting, as well as some strategies for dealing with this challenging clinical dilemma.

Prevalence of Pain in the Intensive Care Unit (ICU)

Although often unable to communicate because of the severity of their disease process or the presence of impediments such as artificial airways or endotracheal tubes (ETT), patients admitted to the ICU often experience pain and discomfort that goes unrecognized and untreated. Estimates vary based on patient populations, but large proportions of both medical and surgical patients report experiencing pain while in the ICU.[1–4]

One study of cancer patients found that between 55% and 75% of patients reported experiencing pain, discomfort, anxiety, sleep disturbance, or unsatisfied hunger or thirst.[5] Another study demonstrated that 77% of cardiac surgery ICU patients recalled experiencing pain, with 64% rating the pain as moderate or severe.[6] An often-underappreciated source of pain in the ICU is during routine procedures, such as patient turning, ETT suctioning, chest tube removal, arterial or venous line insertion, or wound care.[2] One prospective cohort study of 400 medical ICU patients found that those patients for whom analgesics were prescribed had a higher concomitant incidence of hemodynamic monitoring, greater use of neuromuscular blocking agents, more mechanical ventilation days, and more prolonged ICU and hospital lengths of stay.[7] Consistent with these findings, patients who received analgesics also had higher Trauma Injury Severity Scores and predicted mortality.

The SUPPORT investigators examined more than 4000 ICU patients over two years. Family members reported moderate to severe pain at least half the time for 50% of conscious patients who died in the hospital.[8] Similarly high rates of moderate to severe pain were found in another study of surgical ICU patients.[9]

One investigation used a questionnaire to collect data on patients' stressful experiences associated with being in an ICU and on mechanical ventilation.[10] Of those who remembered the ETT, a large proportion were significantly bothered by not being able to speak (68%), pain associated with the ETT (56%), and anxiety regarding the ETT (59%). It is not surprising that this study found that those who did not remember the ETT or ICU were on average more severely ill and subject to a longer duration of mechanical ventilation than the group who remembered these experiences. Given the severity of their disease process, the former group may have been more likely to be chemically paralyzed or heavily sedated.

Despite a high incidence of pain in ICU patients, studies find that it often goes untreated. An observational study in 128 Italian ICUs of 661 postoperative patients found that 36% of patients did not receive any analgesia in the first 48 h of their ICU stay.[11] "Pain control" was listed as the reason for administration in only 54.5% of instances in which an opioid was given.

Barriers to Pain Assessment in the ICU

Given the potential compromise of patients' physiologic stability and communication skills secondary to underlying disease processes, ICU patients present unique challenges for the assessment and treatment of pain. Indeed, critically ill patients have a much higher risk of enduring untreated pain because they often cannot communicate their level of discomfort because of altered mental status, mechanical ventilation, and sedation (Box 81.1).[12] A clinician's observation and subjective rating of ICU patient pain often underestimates that patient's pain.[13] Thus whenever possible, ICU patients should rate their own pain. Patient self-reported pain using a one to ten point numeric rating scale (NRS) has been recommended by critical care societies.[4,14]

A critically ill patient may be obtunded secondary to the underlying disease process or physiologically compromised by a process such as sepsis or shock. The question of how much pain the patient is experiencing may be difficult to answer in these settings. Many patients may not remember these experiences, and even if these experiences can be recalled, there are limitations to assessing pain retrospectively.[15] The use of proxy assessment for patient symptoms is controversial. Proxies, such as family members or bedside clinicians, may overestimate or underestimate the symptoms experienced by patients.[16,17] Therefore increased vigilance by physicians and nursing staff and the development and

• BOX 81.1 Barriers to Pain Assessment and Treatment in the Intensive Care Unit

- Severe critical illness causing altered mental status
- Endotracheal intubation or non-invasive positive pressure ventilation (BiPAP or CPAP mask)
- Failure to recognize or prioritize pain control amid hemodynamic instability, sepsis, or other organ problems

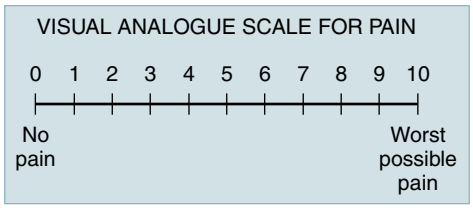
use of alternative means of pain assessment are necessary when patients cannot verbalize pain.

Indirect methods of evaluating pain are used for patients unable to communicate verbally. The behavioral pain scale (BPS) (Fig. 81.1) and the Critical Care Pain Observation Tool (CPOT) are commonly used pain scales used in adult patients, excluding those with brain injuries.[2,3] The BPS uses a patient's facial expression, upper extremity movements, and compliance with the ventilator as surrogate indicators of pain, with a score of five or greater indicating unacceptable levels of pain. Similarly, the CPOT evaluates facial expression, body movements, muscle tension, and compliance with the ventilator for intubated patients or vocalization for extubated patients. A CPOT score of three or above indicates significant pain.

Various studies to validate these tools in the critically ill have been published,[18–20] although other scales, such as the adult Nonverbal Pain Scale (NVPS), and the Faces, Legs, Activity, Cry, and Consolability scale, have also been used in different patient populations.[12]

Pain assessment and treatment can also be systematically improved in ICUs. One study examined the assessment and treatment of pain in two surgical ICUs in a university hospital setting.[21] After the investigators implemented a series of measures to introduce a modified visual analog scale (VAS) similar to an NRS (Fig. 81.2) and educated physicians and nurses on the importance of pain assessment and treatment, pain assessments improved from a rate of 42% to more than 70%. Patients whose pain was controlled (VAS less than 3/10) increased from 59% to greater than 90%. Another study showed that after standardized implementation, the CPOT resulted in a more consistent assessment of pain in critically ill patients and fewer analgesic and sedative agents being administered.[22]

The treatment of pain in critically ill and postoperative pediatric patients is also essential for their comfort, and the use of pain protocols in these regards improves patient comfort.[23] More implementation of such protocols may be helpful in the pediatric critical care population.



• Figure 81.2 Modified Visual Analog Scale for Pain.

Barriers to Pain Treatment in the ICU

The difficulty of treating pain in those hospitalized in the ICU has been documented, and there is a defined lack of high-level evidence for clinical decision making in these regards. Frequent need for rapid drug titration can contribute significantly to interpatient variability in response, which is likely more magnified in critically ill patients. Moreover, there can be significant difficulty in distinguishing adverse drug events from other comorbid medical conditions in ICU patients.[24]

A consensus guideline regarding sedation and analgesia in dying critically ill patients[25] (Box 81.2) recognized the difficulty of pain assessment in this setting as a result of several factors, including communication problems particular to the ICU environment, the severity of the critical illness, the potential presence of multisystem organ failure, the possibility of a decreased level of consciousness resulting from illness and drugs, and difficulty in the interpretation and reporting of clinical signs.

One study analyzed the adequacy of pain control for 17 trauma patients during the initial aspect of their ICU admission.[26] In contrast to the 47% of patients rating their pain as severe, 95% of house staff and 81% of nurses reported the patients had received adequate pain control. This is underscored by the fact that 53% of house staff did not ask patients if pain control was satisfactory. Presumed barriers to adequate pain control were felt to include a disparity in the perception of pain between patients and caregivers, patients refusing to request pain medicine despite the presence of moderate to severe pain, and physician and nurse concerns about patients' adverse physiologic response to further or increased doses of analgesics. It was noted that 19% of patients reported a fear of addiction to opioids. Misconceptions regarding opioid pharmacology on the part of caregivers have been reported.[26] In one report, some nursing staff felt that the use of anxiolytics negated the need for larger doses of opioids.

More recently, the opioid epidemic in the United States has increased scrutiny of iatrogenic, including ICU-acquired, opioid dependence, or opioid use disorder. Studies on the subject are still limited,[27] but in part because of concern about quantity and prevalence of opioid use in the ICU, there has been greater interest

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering) e.g.	2
	Fully tightened (e.g., eyelid closing) e.g.	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

• Figure 81.1 Behavioral Pain Scale.

• BOX 81.2 Guidelines for Relief of Pain and Suffering in the Intensive Care Unit

Relief of Pain and Suffering

To relieve pain and suffering at the end of life, both pharmacologic and nonpharmacologic means should be used. Nonpharmacologic interventions include ensuring the presence of family, friends, and pastoral care (if desired) and changing the technologic intensive care unit (ICU) environment to a more private and peaceful one.

Initial Dosage

Most ICU patients require narcotics and sedatives to ease the pain and suffering associated with their critical illness. The amount of drugs needed varies on an individual basis. As in active disease treatment, palliative care *must* be individualized.

Titration of Analgesics and Sedatives

Once analgesics and sedatives are initiated, they are increased in response to (1) the patient's request; (2) signs of respiratory distress; (3) physiologic signs - unexplained tachycardia, hypertension, diaphoresis; (4) facial grimacing, tearing, vocalizations with movements, turns or other nursing care; and (5) restlessness.

Does a Maximum Dose Exist?

No maximum dose of narcotics or sedatives exists. The goal of palliative care is to provide relief of pain and suffering, and whatever amount of drugs accomplishes this goal is the amount needed for that individual patient.

Should Analgesics and Sedatives Be Administered in Response to Signs and Symptoms of Pain and Suffering or Before They Begin?

Support for both approaches exists among intensivists. The treatment of signs and symptoms of pain and suffering is good palliative care. When appropriate doses of narcotics and sedatives are used, and the intent of the physician is clear and well documented, pre-emptive dosing in anticipation of pain and suffering is not euthanasia or assisted suicide but good palliative care.

Summarized from: Hawryluck LA, Harvey WR, Lemieux-Charles L, et al. Consensus guidelines on analgesia and sedation in dying intensive care unit patients. *MBC Med Ethics.* 2002;3(1):3.

in the use of multimodal analgesia in these patients. In one study of 127 critically ill trauma patients, the implementation of a multimodal approach toward pain control significantly lowered average opioid use without changing average pain scores.[28]

Benefits of Assessing and Treating Pain in the ICU

Patients who are critically ill following surgery are at high risk for pulmonary complications, especially in those who require mechanical ventilation. Pulmonary complications stemming from increased pain may result in hypercarbia, hypoxia, atelectasis, retention of secretions, and pneumonia.[29] Thoracic epidural analgesia (TEA), ultrasound-guided peripheral nerve blocks, and intravenous (IV) patient-controlled analgesia (PCA) may be used in these situations. Clinical scenarios in which placement of thoracic epidurals for analgesia may be of significant benefit include patients with post-thoracotomy pain,[30,31] trauma patients suffering from rib fractures, and to facilitate weaning from mechanical ventilation.[32] PCA, either via the epidural or IV route, can be helpful in an awake and alert ICU patient by allowing the patient to receive on-demand dosing of analgesics, which may reduce the risk of undertreating pain compared to intermittent doses delivered by healthcare providers.

Some controversy exists regarding the efficacy of the administration of epidural opioids, local anesthetic infusions, intercostal nerve blocks, or IV opioids in reducing postoperative pulmonary complications. A meta-analysis of randomized, controlled trials examined postoperative analgesic therapies and their effects on pulmonary outcomes.[33] Epidural opioids decreased the incidence of atelectasis but did not have a statistically significant effect on the incidence of pulmonary infections or other pulmonary complications as compared to systemically administered opioids. Intercostal nerve blocks also did not demonstrate a statistically significant outcome toward reducing pulmonary complications after surgery. In contrast, local epidural anesthetics, compared to systemically administered opioids, were found to decrease the incidence of pulmonary infections and pulmonary complications overall. No clinically or statistically significant differences were found in other measures of pulmonary function, including forced expiratory volume in 1 s, forced vital capacity, or peak expiratory flow rate for any pain management modality. This meta-analysis suggests the value of postoperative epidural analgesia in reducing postoperative pulmonary morbidity compared to other modalities.

The mechanisms of pain's role in the body's stress response include activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, increasing the secretion of catecholamines and catabolic hormones such as glucagon and cortisol, decreasing the secretion of anabolic hormones such as insulin, and increasing antidiuretic hormone and aldosterone levels.[34] Thus one benefit of effective pain management in the critically ill may be to attenuate this stress response.

Pain management in the critically ill is especially important for patients who are dying. One group attempted to study the quality of the dying process in the ICU by retrospectively interviewing family members of 38 ICU decedents.[35] The investigation found that family members perceived that the patients experienced substantial physical symptoms during the last week of life but felt that pain was well-controlled less than half the time. A review of the hospital records showed a nearly universal absence of data regarding pain assessment and records of how sedatives and analgesics were titrated to pain and symptom relief. Of the many items measured, the perception of how well the patient's pain was under control correlated strongly with the quality of dying ratings as measured in the study. Thus optimizing pain management for end of life care supports patients and their families to achieve dignity, respect, and peace during the dying process.

Implementing a structured and scheduled approach to pain management in the ICU may also be of significant value, both to the patient and medical institution providing care.[14] ICU patients whose pain regimens were titrated based on standardized sedation, analgesia, and delirium scores attained better analgesia, received fewer opiates, and endured a shorter duration of mechanical ventilation despite comparable sedation.[36] In patients after cardiac surgery, when "as needed" analgesics were changed to scheduled, around-the-clock dosing with doses prior to procedural pain, pain relief was found to be effective in 95% of patients over the first six days postoperatively. Side effect profiles improved, and median length of stay after surgery decreased. In addition, implementation of a structured ICU pain protocol reduced the cost per patient by $10,500 by decreasing ventilator and ICU days, leading to a cost savings of nearly $2 million for the hospital over 26 months.[37]

Methods of Pain Control in the ICU

This topic is limited to a discussion of methods of pain control (Box 81.3) as pertinent to the ICU setting, given that these issues are discussed in detail in other chapters in this text.

• BOX 81.3 Multimodal Pain Control in the Intensive Care Unit

- Opioids (short and long acting)
- Narcotic Sparing Agents
  - Nonsteroidal anti-inflammatory drugs
  - Acetaminophen (paracetamol)
  - *N-methyl*-D-aspartate receptor antagonists (ketamine, methadone)
  - Gabapentinoids (pregabalin, gabapentin)
- Regional Analgesia
  - Neuraxial (epidural and intrathecal) local anesthetics and opioids
  - Peripheral nerve blocks (including sympathetic nerve blocks)
  - Myofascial plane blocks
- Pre-emptive strategies before major surgery
- Nonpharmacologic approaches (i.e. hypnosis)

Analgesia may be administered by blocking afferent impulses carried along neural pathways, affecting integration in the central nervous system (which may display plasticity and central sensitization in response to pain), and blocking efferent impulses modulated by the neuroendocrine or sympathetic nervous system.[38]

Opioids mediate analgesia by binding with central and peripheral opioid receptors, with the μ and κ receptors most important for analgesia. An "ideal" opioid would have a rapid onset, ease of titration, lack of accumulation of the drug or its metabolites, and low cost.[39] Morphine has ideal characteristics but may precipitate histamine release and theoretically cause hypotension in the ICU patient with decreased intravascular volume. In addition, active metabolites such as morphine-3- and morphine-6-Glucuronide may accumulate in the presence of renal insufficiency. Meperidine is a poor drug for use in the ICU. It is metabolized to normeperidine, the accumulation of which may lead to delirium and seizures in patients with renal compromise. Opioids are discussed in more detail in Chapter 48.

The Society of Critical Care Medicine put forth practice parameters with regard to the use of opioids in the ICU.[40] The authors suggested that morphine is the initial agent of choice and is best started at a loading dose of 0.05 mg/kg administered over 5–15 min. It was suggested that most adults require 4–6 mg/h after an adequate loading dose. This report also suggested that fentanyl (1–2 mcg/kg/h after one or more loading doses of 1–2 mcg/kg) or hydromorphone (initiated at 0.5 mg and titrated by 0.5 mg increments to a general range of 1–2 mg every 1–2 h) are acceptable alternatives to morphine. It is important to emphasize that opioid-tolerant patients often require higher doses of opioid analgesia than their opioid-naïve counterparts.

The use of opioids may lead to hypotension in patients with intravascular volume compromise or those reliant on sympathetic tone for end-organ perfusion, which may be a significant issue in the ICU population. The route of administration is important. Subcutaneous and intramuscular injections, never optimal for pain relief in any setting, are not advisable given the uncertain perfusion and absorption seen in many ICU patients.[41] Transdermal fentanyl presents similar issues and is suboptimal for acute pain management given the 12–24 h delay in both the onset and offset of analgesia.[42] Patients who can cooperate may benefit from the institution of IV PCA. IV PCA possesses an inherent safety mechanism, as the patient will become unable to use the demand feature when side effects such as sedation are more prominent. This property of IV PCA helps minimize the chance of opioid overdose and resultant respiratory depression while optimizing the timely delivery of an analgesic agent to the patient.[43]

In addition to short acting opioids, long acting opioids like methadone may be useful in critically ill patients. Methadone may be particularly helpful for patients on high doses or escalating doses of short acting opioids, though QTc duration should be carefully monitored for prolongation during therapy.[44]

Another adjunct in the multimodal approach to pain in the ICU is acetaminophen. Among older patients, those who received scheduled acetaminophen postoperatively in conjunction with either a propofol or dexmedetomidine drip were shown to have reduced in-hospital delirium when compared to a placebo.[45] Other non-opiate analgesics, such as ketamine in the form of a continuous infusion, may also be useful for critically ill patients.[14,46] Ketamine can be a versatile agent in the ICU as it can be used as both an analgesic and a sedative.

Nonsteroidal anti-inflammatory agents (NSAIDs) should not be discounted as useful adjuncts in some ICU patients. Ketorolac, an IV NSAID, has been shown to have opioid-sparing effects and therefore may limit opioid-mediated side effects. This and other nonselective inhibitors of cyclooxygenase (COX) may have adverse effects on gastric mucosal perfusion, platelet aggregation, and renal perfusion in patients with suboptimal intravascular volume status. Therefore it is recommended that ketorolac be limited to only five days' use and administered with caution in older adults.[47] Highly selective COX-2 inhibitors are not in common use in the ICU setting and may be inappropriate in older adults, given the documented increase in adverse cardiac events in this population.[48]

The preoperative use of pregabalin has been explored to reduce postoperative opioid requirements. One randomized, double-blind, placebo-controlled trial examined a pre-emptive strategy for reducing opioid consumption in elderly patients undergoing cardiac surgery by pretreating surgical candidates with pregabalin prior to surgery and then for five days after surgery. The group of patients administered pregabalin demonstrated a marked reduction of postoperative opioid consumption, to almost 50%, from the time of extubation to the fifth postoperative day, as compared to those on placebo. Patients treated with pregabalin also experienced a reduced incidence of postoperative confusion on the first postoperative day. However, the time to extubation was 138 min shorter in the placebo group.[49] It is unclear if this effect is unique to pregabalin itself or rather a class effect of the gabapentinoids, in which case gabapentin may also demonstrate similar efficacy.

Opioids may be dosed intrathecally postoperatively before a patient's transfer to the ICU. There is a concern for delayed respiratory depression in these patients, which may require monitoring and affect the timing of subsequent analgesics. Intrathecal opiate dosing was examined in a prospective, randomized, double-blind study in postoperative lumbar spinal fusion patients.[50] Patients were randomized to receive an intraoperative injection of 0.2 mg (group 1), 0.3 mg (group 2), or 0.4 mg (group 3) of morphine into the subarachnoid space under direct visualization. Pain levels at 0 h and 12 h after surgery were significantly higher in group 1 than those in groups 2 and 3. However, the patients in group 3 experienced significantly decreased respiratory rates, with higher $PaCO_2$, than those in groups 1 and 2. There was no difference in reports of pruritus or nausea among the three groups. Some intensivists have suggested that this would argue for 0.3 mg as an optimal perioperative intrathecal morphine dose.

TEA using a local anesthetic, with or without the addition of an opioid, may be helpful for patients with thoracotomy pain or traumatic rib fractures.[32] Alternative regional techniques such as myofascial plane blocks have also been utilized recently in the

setting of traumatic rib fractures. These are discussed in more detail in the subsequent section.

Another potential role for interventional pain procedures in the ICU is in patients with poor distal extremity perfusion. Sympathetic blocks may improve circulation in such situations[51] and can be achieved via a stellate ganglion block for the upper extremity or lumbar sympathetic block for the lower extremity. An indwelling axillary or femoral nerve sheath catheter can also deliver local anesthetic continually, either with or without superimposed patient-demand dosing.[52]

It is particularly important to consider the burn ICU patient population, as pain is often one of their most serious and persistent complaints. As an adjunct approach to burn patients' pain management, hypnosis was demonstrated in one study to reduce pain intensity and anxiety, improve the efficiency of administering opioids, improve wound outcome, decrease costs, and overall improve patient care of burn ICU patients without pharmacologically induced side effects.[53]

Neuraxial Analgesia and Regional Anesthesia in the ICU

Epidural infusions may consist of a local anesthetic only, an opioid only, or both. Combining both drugs allows for the synergy of two mechanisms of action: local anesthetics block sodium channels on the nerve membrane, and opioids act via opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. This combination also minimizes the potential toxicity or side effects from each agent, including seizures or cardiac toxicity from the local anesthetic, and sedation or respiratory depression from the opioid.[54]

Many local anesthetic-opioid combinations include fentanyl. Fentanyl is relatively lipophilic, achieves plasma levels relatively quickly, and tends to affect the neuraxis at or near the level of the spinal cord where it is infused.[55] Morphine, conversely, has relatively hydrophilic properties and tends to ascend cephalad in the neuraxis, potentially contributing to delayed respiratory depression.

The clinical situation in the ICU may dictate the choice of analgesic in the epidural. TEA may be beneficial for pain control in post-thoracotomy patients to treat incisional pain and pain from chest tube sites, which can be particularly difficult to control.[56] As many thoracic surgeries restrict the volume of IV fluids administered intraoperatively, patients may arrive in the ICU concurrently with uncontrolled pain and hypotension. Local anesthetics given via the epidural catheter may worsen hypotension because of a decrease in sympathetic tone. One solution to this problem is to provide an opioid only epidural infusion.[57] Adequate neuraxial analgesia can be achieved without the hypotension that might ensue from a local anesthetic, and a local anesthetic-opioid combination can be used once the patient becomes hemodynamically stable. Of note, while epidural opioids are effective for pain, there may not be any additional benefit for an opioid only epidural infusion over IV opioids with respect to pain scores, return of gastrointestinal function, and length of stay.[58]

A group of authors examined the effect of thoracic epidural bupivacaine-morphine versus IV PCA morphine after thoracoabdominal esophagectomy.[59] The epidural group reported better pain scores on postoperative day one and decreased opioid-mediated side effects such as sedation. There was no effect on ICU length of stay, duration of hospitalization, or mortality. The epidural group also received more IV fluid in the first 24 h, likely related to decreased sympathetic tone and hypotension.

Epidural analgesia has also been utilized for ICU patients with posttraumatic rib fractures. One study compared epidural analgesia to IV PCA in patients with rib fractures after motor vehicle accidents and found that epidurals improved patients' pain scores.[32] Although the patients who received epidural analgesia were older and sustained more rib fractures, their pain scores were significantly lower. Another study examined epidurals in patients with chronic obstructive pulmonary disease undergoing open abdominal aortic aneurysm surgery; it determined that both epidural anesthesia and postoperative epidural analgesia improved postoperative respiratory function and reduced postoperative pain compared to general anesthesia with IV analgesia.[60] Finally, one study comparing TEA to a surgeon-administered intercostal nerve block plus a postoperative IV morphine PCA demonstrated that TEA was associated with superior postoperative pain control and restoration of pulmonary function.[61]

There is evidence that despite the demonstration of efficacy for rib fractures, TEA is underutilized. A study retrospectively examined more than 64,000 patients from the National Trauma Data Bank with one or more rib fractures.[62] The authors found that mortality and pulmonary morbidity increased with the number of rib fractures. It was found that only 2% of all patients with fractured ribs received epidural analgesia. This use was increased in patients who suffered six or more rib fractures. The use of epidural analgesia was associated with a significant decrease in-hospital mortality compared to alternative forms of analgesia.

Regional anesthesia may also have an increasing role in the ICU as well. For example, truncal blocks, like serratus anterior, transverse abdominal plane, rectus sheath, quadratus lumborum, and erector spinae, can be useful tools for effective pain control in the critically ill. Peripheral nerve blocks or catheters can provide long-lasting pain control in patients for whom epidural analgesia may be undesirable or contraindicated.[63,64] Although studies related to truncal blocks in the critically ill are still sparse, an increasing number of reports suggest that they can play an important role in the multimodal pain management of the critically ill. For example, one case report demonstrated the utility of bilateral rectus sheath catheters in a patient requiring an exploratory laparotomy who refused a preoperative epidural.[65] Another randomized, controlled trial demonstrated that patients undergoing open thoracotomies receiving serratus anterior catheters with continuous infusions for 24 h postoperatively had comparable pain scores and rescue analgesic IV morphine doses compared to patients who received TEA.[66] Recently, two case reports have demonstrated the efficacy of the transversus thoracic muscle plane block for patients requiring a median sternotomy for cardiac surgery in both a single-shot and continuous infusion peripheral nerve blocks.[67,68]

Compared to other regional and neuraxial techniques, myofascial blocks have virtually no risk of hemodynamic changes, motor blockade, vascular, or intrathecal injection. Two blocks in particular, the serratus anterior plane (SAP) block, in multiple case reports, and the erector spinae plane (ESP) block, in a retrospective cohort study on patients with rib fractures, have demonstrated a reduction in opioid use (SAP and ESP), improvement in pain scores (SAP and ESP), and improvement in inspiratory volumes (ESP).[69] Although these myofascial plane blocks show promise in their efficacy and side effect profiles, additional studies are needed to elucidate further their precise applicability, safety, and dosing in patients with chest wall trauma.

One major barrier to the more widespread use of neuraxial analgesia and regional anesthesia in critically ill patients is anticoagulation. Many patients may require anticoagulation during their hospital stay. Examples include cancer patients with venous thromboembolism and post-cardiac surgery patients with valve replacements or repairs. It is important to know a patient's anticoagulation status and laboratory values prior to initiation and during the continuation of an epidural or peripheral nerve block. The American Society of Regional Anesthesia and Pain Management (ASRA) provides guidelines for the placement, maintenance, and removal of blocks and catheters for peripheral or neuraxial analgesia.[70] The salient points in the ASRA guideline are discussed in Chapter 74.

Sedation in the ICU

The main indications for sedation in an ICU setting include patient tolerance for ventilation, medical and nursing interventions, and actual patient symptoms.[71] Current practice guidelines recommend a systematic, multimodal approach to optimizing analgesia prior to treating agitation.[14] Before treating anxiety in critically ill patients, it is crucial to identify other organic abnormalities that can contribute to their symptoms. These include hypoxemia, hypoglycemia, hypotension, metabolic disturbances, and drug and alcohol withdrawal. Agitation may lead to harmful sequelae such as breathing against the ventilator, increased oxygen consumption, and removal of monitoring devices and catheters.[72] No one gold standard exists to quantify the level of sedation, and the Ramsay, Riker, Motor Activity Assessment, Richmond Agitation-Sedation Scale, and Vancouver scales all have been used for this purpose.[73–77]

Common sedatives used in the care of critically ill patients include hypnotic agents (such as propofol), opiates (including fentanyl or hydromorphone), benzodiazepines (such as midazolam and lorazepam), and centrally-acting α2 agents (most commonly dexmedetomidine). Titrating a given sedative to a defined endpoint has been recommended, with subsequent systematic tapering of the dose or protocol-based daily interruption of sedation with re-titration to minimize prolonged sedation.[14]

Analgesia-based sedation decreased the duration of mechanical ventilation compared to more traditional hypnotic-based sedation during weaning from mechanical ventilation.[78] A remifentanil-based regimen titrated to optimum levels prior to initiation of midazolam (hypnotic agent), compared with a midazolam-based regimen, resulted in a decreased duration of mechanical ventilation by more than two days. It also reduced, by one day, the time from the start of the weaning process to the time of extubation.

One study suggested that dexmedetomidine could be a viable long-term sedative in the ICU setting that may reduce the duration of mechanical ventilation and improve comfort. Two randomized, controlled trials demonstrated that dexmedetomidine was non-inferior to propofol and midazolam in maintaining target levels of sedation in ICU patients who required prolonged mechanical ventilation. Moreover, dexmedetomidine also appeared to reduce the duration of mechanical ventilation as compared to midazolam, and it reduced the time to extubation compared to both midazolam and propofol. Dexmedetomidine was also associated with decreased rates of delirium and improved patient communication with nursing staff compared to propofol. However, dexmedetomidine use did not affect the length of ICU or hospital stay and was associated with higher rates of hypotension and bradycardia compared with midazolam.[79] A more recent study found that patients who received dexmedetomidine as their sole sedative had a similar mortality rate at 90 days compared to patients sedated with propofol or benzodiazepines. However, there were more adverse events reported in the dexmedetomidine group. A significant proportion of the group also required the addition of propofol, midazolam, or both to achieve target levels of sedation, suggesting that dexmedetomidine may sometimes be inadequate as a single sedative for mechanically ventilated patients.[80]

Conclusion

The assessment and treatment of pain in the critically ill patient population are challenging tasks given the frequent lability in patients' physiologic status and the compromise in their ability to communicate. Intensivists have various therapeutic options available, including NSAIDs, acetaminophen, opioids, ketamine, and neuraxial and peripheral nerve blockades. Although undertreatment of pain in ICU patients is well documented, data suggest that organizational changes, implementation of standardized pain regimens and sedation/analgesia protocols, and appropriate use of pharmacologic therapy may improve pain control in critically ill patients. Appropriate sedation is equally important in pain control, and newer agents such as dexmedetomidine, promising shorter ventilation times and better comfort, offer more options to accomplish these goals.

Key Points

- Pain in the critically ill patient is often difficult to assess because of communication barriers and often-life-threatening, multiorgan disease.
- As part of a protocol-based approach, the use of behavioral scales should be utilized in the critically ill to quantify pain and guide analgesia and sedation.
- Pain control is an essential component of care for these patients, and several analgesic therapies are available to clinicians.
- Among opioids, morphine, fentanyl, and hydromorphone are all reasonable initial agents.
- Adjuncts in the pharmacologic management of pain include acetaminophen, NSAIDs, dexmedetomidine, and ketamine.
- Sedatives are frequently used in the ICU to increase patients' tolerance to mechanical ventilation and medical interventions. Medications for this purpose include propofol, opiates, benzodiazepines, and dexmedetomidine.
- Regional anesthesia can be utilized to reduce opioid and sedative requirements.
- TEA and intercostal nerve blocks have been employed for years in the ICU. Newer regional blocks include transversus thoracic muscle plane, rectus sheath, SAP, and ESP blocks. The benefits of these blocks include simplicity of placement, decreased risk of hemodynamic changes, and increased flexibility in the setting of anticoagulants.

Suggested Readings

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Pain Management at the End of Life and Home Care for the Terminally Ill Patient

DALYA ELHADY, DIANE NOVY

Introduction

The end stages of life bring a host of challenging symptoms and causes of suffering that may have accumulated with chronic, progressive, life-limiting diseases. The symptoms of pain, dyspnea, fatigue, and loss of mobility accompany emotional states, such as depression, anxiety, and a sense of uselessness.[1] Of the many symptoms experienced by those at the end of life, pain is one of the most common and most feared.[2] Pain is often undiagnosed and undertreated and can undermine the quality of life and interfere with physical functioning and social interactions. Uncontrolled severe pain is strongly associated with heightened psychological distress and can lead to a desire for hastened death.[3–5]

Improving the quality of life and decreasing undesirable symptoms are the hallmarks of palliative, hospice, and end of life care. Although overlap exists between these models of care, there is a distinction in that palliative care aims to manage and decrease symptom burden because of disease progression of comorbid illness, whereas hospice care is focused on the care and comfort of a patient that is in imminent death or dying.[6] The American College of Physicians defines the end of life period as "a phase of life when someone is living with an illness that will worsen and eventually cause death. It is not limited to the short period when the patient is moribound."[7] This challenges providers to think about the management of pain at the end of life as a chronic symptom as many of these patients will spend significant time in this phase of their life.

Pain associated with terminal illness and end of life is an extremely stressful experience for both patient and family. The prevalence of pain is reported in up to 80% of patients and increases toward the end of life.[8] Additionally, the assessment and management of pain are made more complex by the presence of other symptoms and dynamic changes associated with disease progression. Compared to cancer patients that die in a hospital, those who die at home have a higher quality of life scores, and their bereaved family members are at less risk for developing psychiatric illness.[9] The majority of patients and families prefer to die at home, but there is a minority that prefers to die in the hospital or has no preference.[10] Vidal et al. suggest that preference for dying in the hospital may be attributed to previous failed attempts at home care, uncontrolled symptoms, or caregiver burden.[10] The experience of pain at the end of life involves the management of multiple symptoms by family and friends, which predominantly occurs as a home experience that has potential for improvement.[11]

Pain associated with the end of life and terminal illness is complex and must be viewed within a cluster of symptoms that need to be monitored and managed by the caregiver, which will also require guidance and support from the healthcare team. The successful care of a patient in the final stages of a terminal illness at home is dependent on the awareness and provision of basic and specialized interventions to ensure patient comfort and prevent prolonged grief in surviving loved ones. Careful discharge planning followed by regular assessment and reassessment can facilitate effective pain management and support for the patient at home and minimize pain "emergencies." Effective communication between the primary physician, advanced practice nurse, home care nurse, social worker, and caregiver, as well as ready access to the point person among these professionals, is essential for the success of the home care plan. Input from consulting physicians, such as pain medicine, palliative care, and psychiatry, must also be incorporated in the treatment plan (Box 82.1). A system of ongoing monitoring and support for the patient and caregiver needs to be in place to ensure the effectiveness of pain relief measures and early identification of caregiver burden and unmet needs.

Prevalence and Causes of Pain at the End of Life

It is important to acknowledge and address the prevalence of pain in the end stage conditions that affect patients with advanced medical illnesses, such as cancer, heart disease, human immunodeficiency virus (HIV) disease, neurodegenerative diseases, and end stage renal, liver, and respiratory diseases (Box 82.2).[12] The management of these patients is complicated by the potential presence of multiple comorbid disorders that may each contribute differing components of the overall pain and require separate treatments. Although pain at the end of life is often attributed to terminal illness, common chronic pain conditions are more likely to contribute to discomfort. An observational study of over 4,700 older adult decedents found the prevalence of pain in the last month of life to be 60% in those with arthritis versus 26% in those without.[13]

The prevalence of pain in the terminally ill varies by diagnosis and demographics. Approximately one-third of the people who are actively receiving treatment for cancer and two-thirds of those with advanced malignant disease experience pain.[14,15] Almost 75%

• BOX 82.1 Multi-disciplinary Healthcare Members for End of Life Care

Primary Members	Consulting Members
Primary care physician	Consulting physicians: pain medicine, palliative care, psychiatry
Advanced practice nurse	Specialized nurse: bowel care, wound care, psychiatric care
Home healthcare nurse	Chaplin
Social worker	
Patient	
Patient's caregiver	
Patient's family members	

• BOX 82.2 Common Causes of Persistent Pain in Advanced Medical Illness

- Cancer
- Heart disease
- Human immunodeficiency virus
- Neurodegenerative diseases
- End stage renal disease
- Liver disease
- Respiratory diseases
- Diabetes
- Low back pain
- Osteoarthritis
- Osteoporosis
- Previous bone fractures
- Rheumatoid arthritis
- Shingles; postherpetic neuralgia
- Trigeminal neuralgia
- Peripheral vascular disease
- Central or peripheral neuropathies

of patients with advanced cancer who are admitted to the hospital report pain on admission.[16] In a study of cancer patients who were very near the end of life, pain occurred in 54% and 34% at four weeks and one week prior to death, respectively.[17] In an outpatient cancer center, an evaluation of over 5,000 patient encounters where the pain intensity scores were high (7–10 on a scale of 0–10) demonstrated that 29% of these patients were hospitalized within 30 days of those visits. In another study of more than 13,000 cancer patients in United States nursing homes, an average of 30% of the patients reported daily pain. In those patients, pain varied according to age, sex, race, marital status, physical function, depression, and cognitive status.[18]

In patients admitted to palliative care units, pain is often the dominant symptom, along with fatigue and dyspnea.[12] Until recently, it was widely believed that patients dying from nonmalignant disease did not have high levels of pain. However, it is now known that patients dying from cardiac failure, chronic obstructive pulmonary disease (COPD), end stage renal disease, and other end stage diseases suffer similar levels of pain to those found in patients with malignant disease.[3] Comparing advanced cancer patients to those with symptomatic congestive heart failure (CHF), it is now clear that the symptom burden is as great or greater in the latter.[4] In a multi-center Veterans Administration (VA) study of CHF patients, it was noted that over 55% of them had pain (the majority of which rated their pain as moderate to severe), which was more common than the sensation of dyspnea.[5]

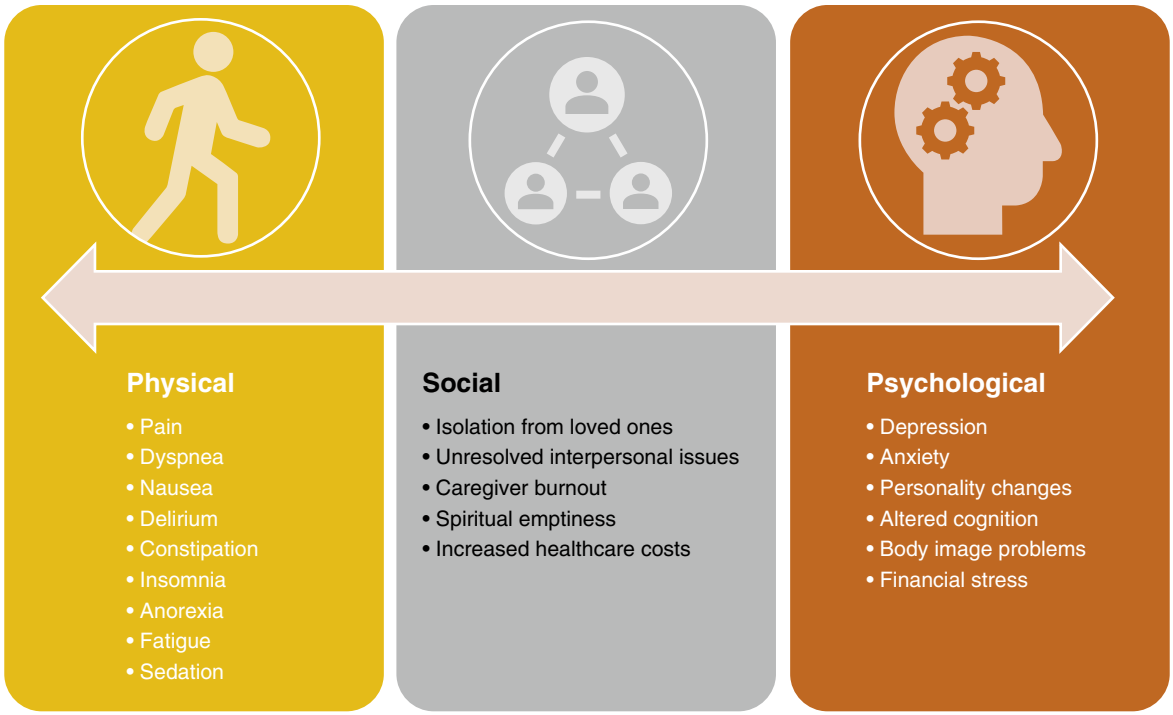
An attempt has been made to characterize the pain experience of those with HIV disease because of the frequently for this disorder to be seen in palliative care settings. More than 56% of patients with HIV disease report pain, with the most common manifestations being headache, abdominal pain, chest pain, and neuropathies.[6] There have been many reports of undertreatment of patients with HIV disease, including those patients with a history of addictive disease.[19] Other groups at particular risk for undertreatment of pain include older adults, minorities, and women.[20]

Assessing Pain and Suffering at the End of Life

Pain remains a subjective experience with physical, psychological, and social dimensions that are interdependent and intensified at the end of life. This multifaceted pain experience significantly impacts patients and families, especially when pain is not adequately controlled (Figure 82.1). Assessment of pain generally includes a thorough history, physical examination, and psychosocial assessment. This serves as a comprehensive guide in the choice of diagnostic studies and the development of a pharmacologic and nonpharmacologic treatment plan. Various assessment tools range from simple unidimensional tools, such as pain rating scales, to complex multidimensional tools that address multiple facets, including physical and psychological symptoms, functional status, mental health, and social role. A systematic review of assessment tools related to palliative care found 152 different tools that primarily identified domains such as physical, psychiatric, social, and end of life care but few existing for spiritual, cultural, and legal domains.[21]

The use of self-report is the gold standard for pain assessment.[22] Ideally, an assessment tool that is suitable for a patient's ability to self-report should be utilized to engage the patient in the evaluation. Older patients or those that are medically frail or terminally ill have a higher incidence of cognitive impairment, hearing and visual deficits, and medication side effects than those in younger or healthier populations. This may complicate the assessment of pain and requires additional time to allow for effective communication. Speech should be clear and unhurried; words and questions should be rephrased to ensure they are understood. The patient should be allowed plenty of time to ask and respond to questions. Some assessment tools such as the Verbal Descriptor Scale (pain thermometer) are validated as self-report instruments for unidimensional pain intensity in patients with mild to moderate cognitive impairment.[23] Many patients near the end of life cannot provide detailed descriptions of their pain character, intensity, or location. Particularly for patients with cognitive impairment, self-assessments may be a burden to complete and difficult to interpret. For patients who cannot self-report pain intensity and description, observational pain assessment tools have been developed to be used by healthcare providers and caregivers. Utilization of available assessment tools such as those listed in Table 82.1 may help in the appropriate assessment of pain even in patients with limited cognition and communication.

Terminally ill patients may complain of pain as a way of expressing other forms of suffering, distress, grieving, anxiety, or depression. Patient behavior suggestive of psychosocial or spiritual concerns require different interventions that will likely be more effective than analgesics. It is well established that attention and emotion influence pain processing and perception, and conversely, inadequately managed pain can lead to anxiety and depression.[15]



• **Figure 82.1** Pain at the end of life has many interactive components, including physical, psychological, and social aspects. Pain that remains inadequately controlled can significantly affect the quality of life for a patient, caregiver, and family.

TABLE 82.1 Assessment Tools for Pain and Suffering at the End of Life

Pain Assessments	Examples
Self-report	Visual Analog Scale (VAS) Verbal Rating Scale (VRS) Numeric Rating Scale (NRS) Faces Pain Scale (FPS) Verbal Descriptor Scale – Pain Thermometer Pain Drawing
Observational	Abbey Pain Scale (patients with dementia, cognition, or communication issues) Doloplus-2 (elderly with communication problems) Pain Assessment in Advanced Dementia Scale (PAINAD) Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) Checklist of Nonverbal Pain Indicators (CNPI) Pain Assessment for Dementing Elderly (PADE) Clinical Utility of the CAN Pain Assessment Tool (CPAT)
Pain-related factors	Multidimensional Pain Inventory (MPI) Edmonton Symptom Assessment Scale (ESAS)
Reports from caregivers	Pain reports of changes in intensity, frequency, location, response to therapy Pain observations of facial grimacing, guarding, tearfulness, agitation

Therefore a comprehensive assessment is required to determine the optimal plan of care, as specific to the pain etiology as possible. The involvement of other disciplines (e.g. nursing, social work, psychology, psychiatry, and chaplaincy) can be very valuable in uncovering other sources of emotional or spiritual suffering that may be confusing the pain assessment. Another invaluable contributor to the assessment of the patient and an important part of the healthcare team will be the patient's primary caregiver.

As increasing numbers of patients are choosing to be home for their end of life, family caregivers assume the majority of patient care.[24] When the patient is being cared for at home, the physician frequently relies on second- or third-hand information supplied by the patient's caregiver on the severity of the pain, adequacy of relief, presence of side effects, and associated toxicity. The correct interpretation of the patient's and caregiver's report of pain is essential since effective pain management is dependent on an accurate assessment. Three dimensions comprise a patient's pain experience: cognitive factors (including attitudes, beliefs, and knowledge), sensory or physical input, and affective or emotional experience.[25] Although patients and families report parallel perceptions of the patient's cancer pain, family members consistently assess the patient's level of pain somewhat higher than the patient. This suggests the effect of observing rather than experiencing the pain. Studies of concordance between caregiver and patient experiences primarily exist for cancer patients only.[24] Engelberg et al. found higher concordance for observable experiences such as breathing and comfort and less concordance with subjective patient experiences such as anxiety and depression.[26]

There are important implications for evaluating the efficacy of a pain management strategy if the assessment is largely dependent on a proxy reporter for the patient. The report of poorly controlled pain may be indicative of the family member's distress and that of the patient. Areas of family distress include fatigue, lack of knowledge about pain management, concern about addiction, concern about harming the patient, and an overwhelming feeling of responsibility.[27,28] The family may interpret the patient's symptoms through their individual concerns, whereas the patient may be able to cope with their symptoms anticipating their own end of

life. Some studies have reported an inverse relationship between the health and function of the cancer patient and the amount of caregiver burden with caregiver strain, depression, and anxiety reaching its peak as the patient enters the terminal phase.[29]

Caregiver concerns and patient distress must be addressed if pain is to be adequately managed in the home as there is a close relationship between the two. Healthcare professionals who depend on caregiver reports in managing patient symptoms must keep in mind the possibility of disconcordant assessments and the trend toward overreporting by family members.[24] Disconcordance between family and patient provides a clinical opportunity for discussion to optimize wellness and understanding of the dyad. Collaboration and communication between the patient, their caregiver, and their clinician are key components of end of life care and specifically for the management of a patient's pain in the home.

Caregivers on the Front Line at the End of Life

The Role of Caregivers

The majority of patients worldwide wish to spend the end of their life at home surrounded by familiarity. The World Health Organization suggests that an increasing number of patients receiving palliative care at home is cost effective.[30] Caregivers are often family members, but friends and paid aides can also fill this role. Caregivers provide comfort and support in assisting patients with activities of daily living, symptom management, and clinical tasks. Among the responsibilities of the caregiver, pain management has been rated one of the difficult tasks that create frustration and stress for the caregiver.[31] Caregivers are expected to play a primary role in pain relief across all stages of the disease and are frequently given little or no training on how to do so.[28,32,33] In a comprehensive review of 129 quantitative research studies on caregivers and palliative care in the home setting, caregivers reported providing extensive help to dying relatives in the areas of medication and symptom management.[34]

Effective medical management of symptoms, especially pain at the end of life in the home, is a complex set of activities that becomes the responsibility of the caregiver and has the potential to decrease the patient's pain as well as ease the burden on caregivers.[31] Caregivers are responsible for ordering and filling, and paying for prescriptions. They are expected to safely store pain medications, and organize and dispense medications on a fixed dosing schedule or as needed based on their assessment of pain. They have to be skilled in administering medications in the form of injections, inhalers, and eye and ear drops. Also, they are responsible for monitoring infusions, medication quantities, medication effectiveness, and adverse events. Furthermore, they are responsible for communicating about medications and symptoms with the healthcare team. A comprehensive review of over 100 qualitative studies on caregiving at home at the end of life, the general consensus across studies was that caregivers reported a lack of preparation, knowledge, and skills in symptom, pain, and medication management, especially with the technical aspects of medication administration.[35,36] From these studies, it can be concluded that most caregivers rely on nurses or other members of the healthcare team for information related to medications.

Case 1: Caregiver's Role

Misconceptions, Challenges, and Barriers to Pain Management in the Home

Generally speaking, the home environment offers substantial benefits to the patient with a terminal illness, but home care also can result in intense burdens for caregivers resulting in compromised care.[34] Surveys of healthcare providers' perceived barriers to pain management in the home include symptom recognition, adherence to analgesic regimens, failure to report pain, and limited access to care.[37,38] Patients and nonprofessional caregivers reported fears related to addiction, analgesic side effects, and accelerating death. Additionally, religious and cultural beliefs about spiritual suffering can influence and at times contradict the foundation of hospice care, which recognizes each person's "right to die pain-free and with dignity".[39] Understanding the barriers that are faced when treating pain in home care settings can lead professionals to better educate and counsel patients and their families.[40] Because misunderstandings lead to undertreatment, all clinicians involved in the care of patients with advanced illness and pain must be able to differentiate and clearly explain to patients and their families the clinical conditions of tolerance, physical dependence, and the rarity of addiction related to opioid use at the end of life. It also is critically important to be aware that there is no established relationship between titration of opioid analgesics to affect pain relief and timing of death in palliative care or hospice settings.[41,42]

Concerns with pain management in the home have been categorized by Chi et al. into caregiver- and patient-centric issues.[31] Caregivers' functional limitations may include physical and psychological fatigue affecting their caretaking abilities. Caregivers may have misconceptions about opioid addiction or fears that pain medications cause hastening death. They also have fears associated with side effects of pain medications causing increased sedation, confusion, and constipation. This leads to under-reporting and potentially withholding treatment despite planned interventions. Physical and psychosocial demands of ongoing work, family, and financial responsibility can interfere with attention to patient care. Ineffective communication or undefined avenues of communication between the caregiver and the healthcare system have also been identified to cause delayed patient assistance. Caregivers report a lack of knowledge about prescribed medications, including a basic understanding of action, dosing, and side effects. This deficit causes confusion and difficult decisions regarding the choice and timing of medication administration for effective pain management. Some studies have estimated the incidence of non-adherence to pain medications to be as high as 24%–51%.[43] Non-adherence to pain regimen may lead to undertreatment or even potentially dangerous medication errors. Caregiver's organizational skill or the potential for multiple caregivers allows for issues in tracking, recording, and safe keeping of pain medications. Patient-centric issues that affect home pain management related to the patient's inability to verbalize pain, their personal view of the quality of life, how they consider the impact of their actions on their caretakers, and the extent of their physical deterioration.[31] The difficulties that patients and caregivers commonly encounter when trying to put a pain management regimen into place at home are summarized in Box 82.3. They illustrate that patients and caregivers need ongoing support and help with problem-solving to optimize their pain management regimen.

Martha is an 85-year-old woman whose ability to function independently has declined in the past five years. She has end stage renal disease and requires dialysis three times a week. Because of her severe fatigue and chronic non-cancer pain from debilitating osteoarthritis, she is functionally very limited. She also suffers from depression and anxiety. Her only surviving family, three adult children, all work outside of the home and cannot oversee her care during the weekday hours.

Besides her primary care physician and psychiatrist, she also sees a pain specialist and a renal specialist. In addition, she receives 20 h a week of home health care through her insurance provider. Her caregiver, Bridget, has been with her for two years and her responsibilities include taking Martha to her medical appointments, picking up Martha's prescriptions and supplies, and setting up Martha's weekly pillbox. Bridge also helps Martha with bathing and with household chores. Bridget also provides Martha

with companionship and a sense of security, knowing her needs are being addressed. Martha's adult children provide care in the evening hours and on weekends and see to it that Martha feels loved and supported.

Effects of Unrelieved Pain on the Patient and Caregiver

There is growing evidence that inadequate pain relief might hasten patient death, not only via the well-recognized morbid effects of increased physiologic stress, reduced mobility, increased proclivities toward pneumonia and thromboembolism, and increased work of breathing and myocardial oxygen requirements but also through immune suppression.[44] Pain may lead to spiritual despair and significant decrease in emotional wellbeing because the individual's quality of life is impaired. Home care is best viewed as a family experience with the recognition that every aspect of care provided to the patient will not only affect patients but also affect family caregivers. The intense demands on family caregiving at home, especially in the provision of 24 h physical caregiving, is well described.[45] Less attention has been placed on the emotional burden to the family assuming responsibility for the patient's well-being in the home.[46]

Caregiving has been identified as a risk factor for mortality.[47] This carries not only physical consequences but emotional, economic, and social implications.[48] Caregivers retain difficult memories of loved ones' uncontrolled pain and suffering. They may have enduring feelings of guilt for having given too much medication that facilitated death or frustration regarding the type of care received. These perceptions impact caregivers' satisfaction with home care of their loved ones, the quality of their bereavement, and their ability to manage pain in the future.[49]

Palliative care and hospice programs provide care for the combined unit of the patient and the caregiver. Understanding the factors that influence the adequacy of pain management in the home has become increasingly important in the face of the current trend toward shorter inpatient hospital stays, earlier hospital discharges, and the expectation that extremely sick patients will be managed at home.[50] Addressing issues with patients and caregivers regarding knowledge and attitudes about the varied etiologies of pain and its management, the stress in caregivers and community nurses, managing the technical aspects of pain in the home, and communication will serve to support families and foster trusting relationships.[51–53] When pain and other distressing symptoms are properly addressed, and advance directives are completed to guide the caregiver, quality scores for end of life care increase, costs and resource utilization decrease, and caregiver stress is diminished.[54–56] The interdisciplinary healthcare team utilizing nurses, social workers, chaplains, physicians, volunteers, and others is imperative to provide education, counseling, reframing, and spiritual care to patients and families exploring the end of life care and barriers to pain relief in the home setting. The recognition that home caregiving and community nursing have necessitated responsibility without adequate training has been an impetus for improved communication and educational programs for pain management at home.

• BOX 82.3 Home Care Challenges that Risk Poor Pain Control at the End of Life

- Complex pain syndromes from comorbidities and advanced disease
- Rapidly escalating opioid requirements and need for an alternative route of drug administration
- Polypharmacy for multiple end of life symptoms
- Impairments of memory, cognition, vision, or hearing
- Fear of opioids because of addiction or side effects
- Under-reported pain because of fear of caregiver burden or hospitalization
- Physiological, psychological, and social fatigue on patient, family, or caregiver
- Inadequacy of pain treatments, non-adherence to the regimen
- Inaccessibility to prescriptions, resources, or healthcare team for changes or emergencies
- Unfamiliarity with medication uses, administration
- Caregiver functional limitations, organizational skills
- History of drug abuse or high risk home environment

Recommendations for Positive Outcomes

Caregivers with community nursing support are on the front line of home pain management. Structured pain education programs have been shown to result in positive outcomes for patients and their caregivers.[37,38] Recommendations include teaching caregivers about the practical aspects of care at the end of life and making sure caregivers were routinely provided with general information about the nature and course of the patient's disease. Patients and caregivers should be asked whether they are concerned about addiction and tolerance (often described as becoming "used to" or "immune" to the drug). Caregivers should be educated on changes in patient behavior such as irritability or frustration that may be cues to underlying pain symptoms. They should also receive education on the symptoms of aberrant respirations, decreased food and water intake, diminished cognition, delirium, low urine output, and incontinence at the end of life phase for a patient who is actively dying.

Care providers have concerns about precipitating death with the use of opioids or benzodiazepines used aggressively during this phase of active dying. It has been established that patients have legal and ethical rights to symptom management during this time.[57] It has been observed that patients live for longer periods when symptom-driven medications are delivered as compared to those without the medications.[58,59] The reason for this is unsettled, but physiologic-based theories have been published. The provider has a duty to address the ethical, legal, and physiologic rationale for medications with patients and caregivers in this situation.

Caregiving is not uniform, and the needs of patients at the end of life and the needs of their caregivers are neither identical nor static. Incorporating a pain log or diary to improve documentation of pain, pain management strategies, and their effects on pain relief can provide concrete evidence to help individualize strategies. Accurate documentation in this manner is even more essential when multiple caregivers are involved in the care of a patient.[43] Caregiver burden and comfort with home pain management regimens must be assessed and reassessed. Essential drugs should be made available at home outside of outpatient healthcare hours to enable rapid symptom management and prevent unnecessary hospitalization. It is the professional and ethical responsibility of clinicians to focus on and attend to adequate pain relief for their patients and properly educate patients and their caregivers about analgesic therapies.

Planning for Home Pain Management

Transition From Hospital to Home

Transitioning patients with a terminal illness from the hospital to a home setting for the end of life care is a challenging task because of the complexities of coordination of care, the types of

interventions, the inadequate management of refractory symptoms, and the lack of caregiver support. Patient care that has been entirely organized by healthcare professionals during the hospital stay without caregiver involvement may cause feelings of inadequate preparation or anxiety during the discharge process as the burden of care and decision making shifts primarily to a sole caregiver. In preparing the patient and their caregivers to go home, the focus should be on security, communication, and clarification of the pain management plan. A review of efficacious home care programs found that linkages with hospital and community services, multi-disciplinary team and holistic care model, and access to the end of life care expertise (including pain and symptom management) were associated with improved outcomes.[60] The outcomes included quality of life, satisfaction with care, performance status, pain management, non-pain symptom management, supporting home deaths, and reduced healthcare costs. The components of the home care program reduced barriers within organizations, increase accountability, facilitate transitions, prevent symptom exacerbation, and avoid an unnecessary end of life hospitalization while providing overall improved quality of life and satisfaction.[60]

Hospital to home transitions should begin with a review of the guidelines and resources provided by The Joint Commission's foundations of safe and effective transitions of care to home and the National Patient's Safety goals for home care.[61] Transition to pain management in the home requires an individualized pain management plan that often benefits from early and recurring discussions of patient goals and values within family meetings with the use of "teach-back" to ensure understanding of the discharge plan. Patients and caregivers assuming responsibility for pain management may have a limited understanding of medical conditions and medications, low health literacy, and lack of confidence in self-care resulting in difficult transitions. Promotion of positive communication strategies between caregivers and staff, ensuring the adequacy of information in preparation for discharge, trying out the role of caregiver, and testing the home environment for barriers with short weekend discharges prior to definite discharges have all been some features of successful transitions to home care.[62]

Assessment of the home care environment and identification of anticipatory needs and potential scenarios for patients that are terminally ill is an integral process to achieve sustainable and satisfactory transitions to home care and to decrease the risk of readmission.[63] Repeated hospitalization and discharge episodes are notorious for interrupting the pain regimens of patients as new treatment teams become involved or new medications are added or withdrawn in light of new medical conditions or side effects.[64] The pain management plan should be appropriate, complete, and clearly written out in a language that the patient and family can understand. Pharmacists can be an invaluable resource in helping with medication reconciliation, assessing routes of administration, reviewing prescriptions for completeness, evaluating for polypharmacy, and the need for non-comfort medications or duplicate therapies.

Medication and therapeutic interventions should be financially feasible for the patient, the availability of prescribed analgesics should be verified in the community, discharge and follow up plans should be confirmed with patient and family, and the patient should not be discharged (if at all possible) within 24 h of a change in opioid drug or route of administration (Box 82.4). Availability and cost of outpatient medication can become a significant barrier for patients.[65] The community pharmacy should be contacted to ensure the availability of prescribed opioid medications or willingness to obtain them.[66] Prior to the patient's discharge home, it is important to establish the ability of a patient to both pay for and obtain their outpatient analgesic prescription. Several pharmaceutical companies have specific patient "hardship" programs for assistance. A social worker can be a helpful resource in evaluating a patient's eligibility for these programs and accessing such resources.

It is good practice for the physician or nurse to initiate contact with the patient within the first week of discharge to confirm that pain is adequately controlled. This acknowledges the central role of the family in the management of pain in the home, emphasizes that the family will be given ongoing support and back-up for their day-to-day pain management decisions, and ensures patient and caregiver confidence with the pain management approach. This initial telephone contact also confirms that pain management is a priority, and the patient's pain will continue to be monitored closely with resources readily available even though care is now on an ambulatory basis. If a patient's pain escalates once at home, it is crucial to explore with the patient or caregiver whether the pain medication is being taken as prescribed and the availability and appropriate use of rescue medications. Close follow up with the family soon after discharge is essential as they are still learning the basic principles and skills required for pain management. Once these skills have been learned and a routine established, the need is for continuing support and validation.

• BOX 82.4 Factors to Facilitate Hospital to Home Transition

Do Not Discharge a Patient

Within 24 h of a change in route of opioid administration.
Within 24 h of a change in opioid drug.
Without written instructions regarding their analgesic regimen.
Without a 24 h resource telephone number for pain management issues.
Without a bowel regimen.

If a Patient is Being Discharged on a Non-parenteral Route of Drug Administration, Make Sure

That the prescribed drugs are available in the patient's community pharmacy.

That the patient has an outpatient prescription plan and, if not, will be able to pay for the pain medication out of pocket.

That the patient is given sufficient medication at the time of discharge to continue on the pain management regimen until the patient can fill the prescription at a community pharmacy.

If a Patient is Being Discharged on a Parenteral Infusion

Avoid sending the patient home on the weekend if possible.

Give the patient a 48 h supply of oral or injectable opioids to take home if there is a mechanical problem with the pump.

Case 2: Transition From Home to Hospital

The Decision for Long Term Care Facility or Hospice Care

Some patients are unable to be cared for at home and are discharged to an extended-care facility. Such facilities include nursing homes and assisted/supportive living facilities. These patients are frequently elderly, debilitated, and receiving polypharmacy for chronic medical conditions. They are at high risk for inadequate pain assessment and consequent under medication for pain.[34] In addition, the elderly and debilitated patient's therapeutic margin

may be narrow, and the patient may be at increased risk for developing troublesome side effects, including sedation and confusion.[67] Close monitoring is required, with careful dose titration and adjustment based on ongoing assessment. This requires training, skill, and an institutional system in place that screens for the presence of pain and adequacy of relief on a regularly scheduled basis. It is essential that verbal communication be established between the physician/advanced practice nurse or pain management nurse from the discharging institution and the physician and nursing supervisor from the extended-care facility. This communication should take place prior to the patient's discharge to the facility. The two teams can then work together to ensure adequate pain relief for the patient. In recent years, some long term care facilities have established contracts with community hospice programs and have developed palliative care approaches to the care of their residents.

Hospice care, the most widely available model of home care for the dying, focuses on optimizing the quality of life in those not seeking and unlikely to benefit from life-sustaining treatment.[68] Hospice programs are run by both profit and not-for-profit organizations and have become part of the standard of care offered to patients nearing the end of life. Eligibility requirements for enrollment in a hospice program include a life expectancy of six months or less. A major advantage for patients and families followed in a hospice home care program is regular home visits by the hospice nurse and 24 h emergency support from skilled hospice nurses with back-up from the hospice medical staff. In addition, the cost of all medication related to the terminal illness is included in the hospice benefit without additional charge to the patient. Because of the variety of hospice models, levels of sophistication, and depth of services offered, the needs of the patient and the services offered through the program should be evaluated before referral. For example, although most hospice programs have changed their policy toward the use of technology in end of life care, in contrast to an earlier "no high-tech" approach, severe restrictions on the financial reimbursement for programs may limit their ability to deliver care to patients requiring the parenteral route of opioid infusion to manage their pain.

Sally is a 21-year-old woman who has suffered from neurofibromatosis and debilitating pain since her early teens. Even as she faced these challenges, she was able to finish high school and establish close friendships. However, in the past year, Sally was found to have a new tumor that is malignant and inoperable. Sally understands that her condition is terminal and now relies on her mother for assistance with activities of daily living.

Sally's pain had been treated adequately with intrathecal hydromorphone delivered by an implanted pain pump. As her disease progressed and her pain has become more severe, she was hospitalized and relied on intravenous hydromorphone in addition to her pain pump. After a three week hospital stay, Sally and her mother are eager to be discharged from the hospital and want Sally's remaining time alive to be spent at home. For this to happen, Sally would have to be off intravenous medications. This was accomplished by titrating the daily rate of intrathecal hydromorphone, transitioning intravenous hydromorphone to oral formulations, and adding adjuvant medications. Also, an assessment was made of Sally's home environment, and there was the identification of specific equipment and supplies that Sally would need. A hospital bed and bedside commode were ordered for her home. Additionally, Sally's mother had to learn techniques and skills to be Sally's primary caregiver at home. Sally's mother learned the necessary skills of how to help her daughter transfer from bed to chair and bedside commode, safe handling and delivery of medications, and communicating with Sally's healthcare team. Weekly telemedicine appointments were scheduled with Sally's pain physician. Face-to-face follow up appointments were to be scheduled as needed. Although Sally and her mother were not ready to have home hospice care at the time of discharge from the hospital, they have started to consider this option for some time in the future.

Discharge to Suspected Drug Diverting Environments

There may be patients who are going home to an environment where it is suspected that drug abuse or diversion may occur. The patients themselves may or may not have a history of illicit drug use. Patients with a history of drug abuse are at risk for having undertreated pain.[69] Three subgroups of patients can be identified: (1) patients who are actively using street drugs, (2) patients who are in methadone maintenance programs, and (3) patients who have not used illicit drugs for many years.[19] Patients with substance use disorders present a challenge in pain management at the end of life because of limited and avoidance of communication, late identification of palliative care needs, and preferences and coping strategies at the end of life that are different from those that are generally accepted.[62,63]

Patients with a history of drug abuse that require end of life pain control require strict monitoring during opioid therapy. It must be recognized that these patients, like any other patients, can experience significant pain but may require larger doses of opioids to control the pain because of the development of tolerance. If the patient is on an oral drug regimen, it may be necessary to give only a one week supply of the opioid at a time. Giving a larger amount at one time invariably results in the patient "running out of the drug" regardless of the amount given. Occasionally these patients are placed on a parenteral route of opioid administration to ensure adequate pain control and safety, maintain tighter control on the amount of drug used, and minimize the risk of drug diversion. In these situations, no extra opioid cassettes or infusion bags are left in the home, and neither the patient nor family is taught how to change the infusion. Infusion cassettes may be preferred over bags because of less risk of "siphoning off" the medication. Close coordination and communication between the prescribing physician or advanced practice nurse, the home infusion pharmacist, and the home infusion nurse is necessary for patients in this scenario.

Psychiatric symptoms and comorbidities such as anxiety, depression, and bipolar disorders are frequently seen in this population and need to be addressed.[69] A team approach with optimal cooperation is essential in the care of these patients.[70] If the patient is in an addiction maintenance program, the program must be contacted for assistance in planning the patient's overall care. One physician or advanced practice nurse should be identified as the point person to adjust analgesics and write all prescriptions, and one nurse should be identified as the person to organize and coordinate the patient's plan of care. Patients with pain who are discharged home to a high risk drug abuse environment encompass a relatively small group of individuals whose needs are more challenging and require creative solutions. However, with careful planning and close monitoring, safe pain management at home can be achieved for most people.[70]

Communication: The Cornerstone of Good Pain Management in the Home

Foundation of Communication

To ensure that the pain management plan instituted in the hospital can be maintained at home, a series of steps can be taken.[61] First, if home care nursing has been established, the home care nurse should be contacted to discuss the pain management plan. Second, the community pharmacy should be contacted to ensure that they have the prescribed opioids in stock, or if not, are willing to obtain the medication. In addition, it should be established specifically when the drugs will be available in the home pharmacy so that the patient is not left uncovered. In the event that the local pharmacy neither has nor can obtain the prescribed opioid, an alternative source for the patient must be located prior to discharge from the

hospital. Third, the physician or nurse practitioner who will be responsible for writing the opioid prescriptions and titrating the drug must be clearly identified. Fourth, the caregiver should be instructed to establish a routine where the amount of medication they have left is checked on a scheduled basis so that the medication does not "run out" (the Friday night and holiday syndrome). Some families find it helpful to keep a one week supply of the medication to the side, and when they need to go into that supply, it reminds them to call their prescribing clinician for a new prescription. These simple steps can help ease the transition from hospital to home for patients with chronic pain and the family.

It is essential that the patient and family are given specific, detailed, written instructions, in layman's language, of the pain management approach to be used, both pharmacologic and nonpharmacologic.[61] The concept that analgesics should be used to prevent pain rather than having to be "earned" through experiencing severe pain is a principle foundation of the pain management approach that should be discussed with patients and family. This principle encompasses addressing the concerns surrounding the prevalence of addiction when opioids are used to manage pain and the clinical significance of tolerance (e.g. that the opioids may no longer be effective if they are used early on in a disease process). The patient and family must have no ambiguity about whom to call on a 24 h basis if pain is not well controlled or if the patient experiences troublesome side effects. In addition, safety issues surrounding opioids in the home need to be reviewed. These include that the opioids be kept in a safe place out of reach of children; that unused opioids be flushed down the toilet or returned to the prescribing institution for disposal; that if parenteral opioids are used, a syringe and needle disposal kit be obtained; and that needles and syringes, however well wrapped, should not be disposed of in household garbage containers.

Continuity of care for patients' end stage illness or cancer with pain is particularly important. Frequently, patients receive their care in various medical settings with the involvement of numerous physicians, nurses, and healthcare professionals who may not have considered pain as a priority. In addition, effective management approaches may be changed because of the patient's or families' unfamiliarity with complicated medication administration, lack of community resources, or concern regarding opioid quantity or side effects. The hospice movement has addressed the need for continuity of care of the dying patient.[68] Similarly, the need to bridge the gap between hospital and community is recognized for the terminal patient with chronic pain who is not imminently dying.[71] A palliative care approach is seen as a valuable component to patient care that addresses the needs of the terminal patient with chronic pain earlier on in the disease process. Such a model of care is also important for dying patients who either do not have access to a hospice program or who, for a variety of reasons, choose not to be followed by the hospice system of care.

Tools of Communication

Effective communication between healthcare providers and caregivers is essential to the successful management of pain at home at the end of life. Identification of appropriate tools to facilitate communication between providers and caregivers should be established prior to or early in the transition period to home. The preferred method of communication and available technology at home should be discussed, as should the expected frequency and limitations to this mode of communication. Patients and caregivers should be encouraged to keep a daily diary to record pain level using a numerical estimate (e.g. a zero to ten scale), or a categorical scale (e.g. none, slight, moderate, severe), medication taken, other pain-relieving strategies used, extent and duration of pain relief, activity level, and interference with quality of life. Keeping a pain diary has been found to heighten patient and caregiver awareness of the pattern of pain, guide pain management behaviors, enhance a sense of control, and facilitate communication.[72]

The use of the telephone is an important aspect of monitoring and managing pain on an outpatient basis.[73] In addition, it makes expert resources available to communities where this might not otherwise be the case. Continuity of care also can be fostered through 24 h telephone availability of a pain management expert (usually an advanced practice nurse) to the patients, their families, and community professionals. Although the availability of after-hours and urgent care remains an integral resource, the utilization of these services was found to be significantly decreased with a model that employs proactive telephone-based communication. This proactive system provides a systematic call frequency and structure of one or two calls a day to each patient with standardized staff script, identification of clinical needs, and escalation of issues to a nurse for effective and efficient home care.[74]

Although the use of the telephone remains a primary mode of communication, advances in technology have made the use of telehealth an emerging option to provide clinical support in the home setting. Digital technology has become ubiquitous in both healthcare and patient homes. Most patients are regularly using computers, tablets, and smartphones with internet connections. Many patients currently use the internet as a resource for knowledge that is easily available and accessible in various formats and use calendar and alarm functions for daily organization. However, there is an opportunity to increase the use of technology for more than just appointment organization and medication reminders. Telehealth can be in the form of video or virtual consultation to facilitate support and continuity of care, digital programs to reinforce education, and the utilization of alternative communication methods such as email, web-based programs, or applications to communicate or document changes in management approach.[75] Advances in telemonitoring can enhance daily symptom management with triggers built to stimulate help seeking, help with reminders or prompts for medication management, or even initiate action by professionals. These tools can be used to personalize monitoring and augment patient-provider communication. Telehealth is regarded as an efficient and cost effective method of communication that improves equity of access to care. However, caution must be taken to utilize digital solutions in a way that adds value to patient care without adding unnecessary burden to the patient, caregiver, and provider.[76]

Case 3: Telemedicine as a Tool of Communication

Pain Management Therapies at the End of Life

How to Approach Pain Management at the End of Life

Patients in the terminal stage of an illness often experience multiple mechanisms of pain. Mechanisms of pain can be categorized into central sensitization, peripheral neuropathic, nociceptive, sympathetically mediated, and cognitive-affective.[77] It is important to differentiate among different types of pain because the type of treatment and its success is largely dictated by the pain mechanism and its original source.[77] In some conditions, especially metastatic cancer, pain is often caused by a complex mixture of nociceptive

and neuropathic factors. The etiology of the pain mechanism then forms the basis of pharmacological treatment strategy, which should be individualized and consider comorbidities, expected side effects, route of administration, and concomitant medication. An important strategy for treating patients, especially at the end of life, is using one medication that might treat more than one type of pain or multiple symptoms. For example, an opioid might be helpful for neuropathic pain as well as somatic pain. Some anti-depressants can be employed for both neuropathic pain and insomnia. This strategy is supported in the medically frail population.[78]

Besides the numerous and sometimes overwhelming responsibilities related to the pharmacologic management of pain in the home, patients and caregivers use many nonpharmacologic strategies for pain relief. Although some of these techniques are taught in the hospital setting, they are seldom reinforced by the medical team once the patient is discharged home. Non-drug interventions include both physical and cognitive approaches. Physical approaches include interventions such as heat, cold, and massage. Cognitive strategies include a variety of relaxation techniques, imagery, meditation, and prayer.[79] These nonpharmacologic therapies should be tailored to individual likes, dislikes, and effectiveness. Knowledge of the various modalities, management of expectations, and open-mindedness will help clinicians identify therapies that fit the patient's values and belief system. The use of these modalities will not only enhance pain relief but also help the patient regain a sense of control.[80] Similar to pharmacotherapy, multimodal approaches offer the potential benefit of additive and synergistic effects.

Buddy is a 75-year-old male with a diagnosis of Stage IV lung cancer. He has chronic non-cancer low back pain as well as chemotherapy induced neuropathic pain. His pain is adequately managed with tramadol and gabapentin. However, his breathing has become more labored and uncomfortable lately and has required continuous oxygen via nasal cannula. He is largely confined to his apartment that he shares with his wife. Because it is very difficult for him to come to his medical appointments, his healthcare team uses telemedicine visits to monitor his pain and health and make necessary adjustments to his medications. Buddy and his wife are reassured during these visits. When necessary, a home nurse may be sent to assess Buddy, and there will be coordination of care with his physicians.

Nonpharmacologic Approaches to Pain Management in Palliative Care

An important aspect of any management strategy is the use of nonpharmacologic treatments. Various nonpharmacologic approaches to pain are effective in alleviating pain for patients with advanced illness.[81] These include physical interventions such as positioning and active or passive mobilization, heat or cold therapy, transcutaneous electrical nerve stimulation (tens), massage; psychological therapies such as relaxation, imagery, or cognitive behavior therapy; and complementary or alternative medicine techniques such as music and acupuncture. Nonpharmacologic interventions often comfort the patient while involving and empowering family and other caregivers. The effect of these techniques on the caregiver should not be overlooked—it can have a direct effect on the experience of the patient as well as the emotional survival of the family caregiver in particular. A study by Keefe and colleagues[40] on the self-efficacy of family caregivers of cancer patients found that caregivers who rated their self-efficacy as high reported much lower levels of caregiver strain as well as lower negative mood and higher positive mood. Caregiver self-efficacy in managing the patient's pain was related to the patient's physical wellbeing. When the caregiver reported high self-efficacy, the patient reported having more energy, feeling less ill, and spending less time in bed. Aside from their objective efficacy, the use of complementary therapies can be an "emotional inoculation" that builds resiliency and an important bond between patient and caregiver.[82]

Rehabilitation and Physical Therapy

Functional rehabilitation and physical therapy techniques in appropriately selected patients can add to the quality of life even in the face of limited life expectancy. Multiple studies assessing the use of physical therapy in the palliative care setting suggest primary benefit in decreasing musculoskeletal pain levels along with improvements in mobility and completion of activities of daily living.[83,84] These studies show that patients who receive physical therapy intervention report increased quality of life and improved mood and confidence. Physical therapists seem to provide educational and physical support to patients and caregivers to maximize the patient ability and achieve meaningful care.

Massage Therapy

Therapeutic massage uses the manipulation of body tissues to affect the neuromuscular and circulatory systems to reduce muscle spasms and aid in relaxation. Massage has also been used in conjunction with aromatherapy to utilize the therapeutic properties of plant essential oils to facilitate physical, mental, and emotional wellbeing. There is good evidence that these therapies may be helpful for the reduction of pain and improvements in anxiety and peacefulness, with statistical significance shown for short periods.[79,85,86] Although studies have not demonstrated significant long term benefits in improving pain control, anxiety, or quality of life, significant improvement in sleep scores and reduction in depression scores were found in one group of patients receiving massage therapy.[87] Findings suggest that patients with high levels of psychological distress respond best to these therapies. Massage therapy is a non-invasive therapeutic tool that can reduce suffering and improve symptom management in advanced illnesses. Restricted sites or therapy may be warranted for patients with open wounds, on anticoagulation, with a recent diagnosis of deep vein thrombosis or diagnosis of multiple myeloma.[86]

Electrophysical Modalities

Transcutaneous electrical nerve stimulation (TENS) is an inexpensive and non-invasive electrical modality that can be used for patients at the end of life with or without active neoplastic disease. Alternative modalities such as therapeutic ultrasound, or interferential or pulsed shortwave diathermy may be used over normal tissue or for non-cancer patients to reduce pain and muscle spasms.[67] Overall improved quality of life, decreased pain, and improved fatigue has been associated with the short term use of TENS in hospice cancer patients.[79] Scrambler therapy is a newer modality that attempts neuromodulation by using electro-cutaneous nerve stimulation to provide cutaneous nerves with "non-pain" information thus blocking the effect of pain. Studies have shown significant, sustained pain reduction with scrambler therapy in neuropathic pain and in patients with and without cancer.[88] Awareness of implanted devices (pumps, stimulators, implantable cardioverter defibrillators, or pacemakers) and precautions to prevent malfunction must be taken with the use of therapies involving electrical stimulation.

Psychotherapy

Simple psychological interventions can have a significant impact on pain. Relaxation techniques may be effective in reducing pain in terminally ill patients. Relaxation with or without imagery can improve pain in patients with oral mucositis, which can often be

a poorly controlled symptom in this patient population.[79] Mindfulness based cognitive therapy in palliative patients resulted in improvements in anxiety, ruminative thoughts, and sleep problems and reduction in depressive symptoms.[89] These cognitive interventions can provide patients and families with support, knowledge, and skills to help cope with pain at the end of life.[67] Patients with delirium and cognitive impairment may not be appropriate candidates to benefit from these modalities of psychotherapy.

Acupuncture

Acupuncture therapy continues to be studied as a complementary therapy in symptom management of pain, dyspnea, and fatigue for palliative patients as well as cancer patients. Acupuncture has been shown to significantly reduce pain with suggested shorter analgesic onset and longer duration of action than conventional medicine.[90] Patients with dyspnea because of cancer or COPD that were treated with acupuncture/acupressure reported marked symptomatic improvement in breathlessness.[79] Although evidence has not shown the effectiveness of this modality, it remains a therapy that is relatively safe with rare complications.

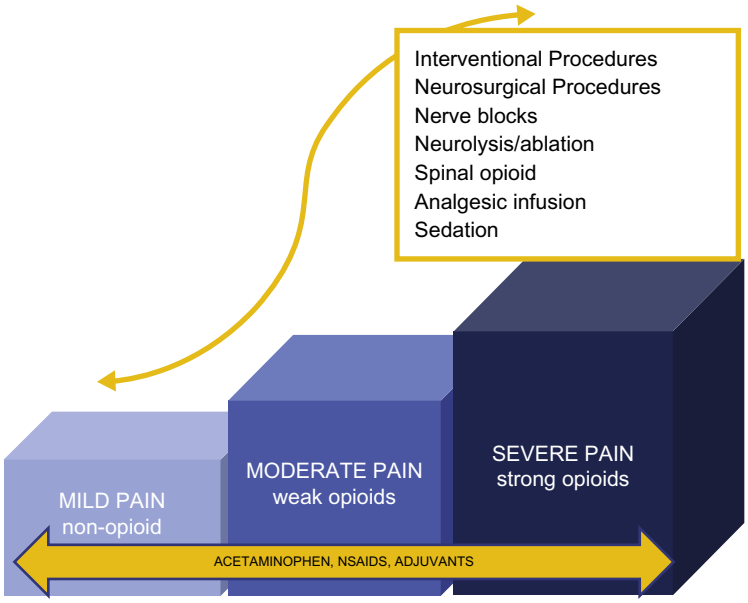
Music Therapy

The therapeutic use of music therapy as an adjunct treatment in cancer and palliative/hospice populations is increasing. Music therapy can improve quality of sleep, quality of life, and symptoms of depression and provide comfort and relaxation.[91,92] Although there is a wide variety of individual preferences, music appears to exert direct physiologic effects through the autonomic nervous system with the release of endorphin from the brain.[91]

Pharmacologic Approaches to Pain Management in Palliative Care

Pharmacologic therapies for pain include non-opioids, opioids, adjuvant analgesics, disease-modifying therapies, and interventional techniques. The World Health Organization pain ladder establishes a stepwise guideline in the approach to pain management. However, the use of this guideline for patients with a terminal illness may delay adequate pain control (Figure 82.2). Patients at the end of life may require strong opioids to achieve effective analgesia and may have contraindications to first line non-opioid therapies such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) because of their advanced illness.[93] Normal pharmacokinetics and pharmacodynamics may be considerably altered by patient age and end stage disease states. For example, in patients with chronic liver disease or hepatic metastases, drugs may bypass hepatic metabolism altogether, increasing bioavailability. Similarly, renal clearance is almost always diminished during the dying process, leading to the accumulation of drug metabolites, some of which may be toxic.[94]

Intractable pain and symptoms that are not responsive to basic therapeutic techniques, although not common, must be treated appropriately and aggressively.[1] In some highly selective cases, palliative sedation may be warranted.[95] Commonly, there is a need to use drugs for non-U.S. Food and Drug Administration (FDA)-approved indications or routes of administration, simply because randomized controlled clinical trials do not exist for that particular circumstance. New formulations or delivery systems are continuously under investigation and approved for market that may have a role in alleviating pain at the end of life medication. No new or renovated analgesic agents have been shown to be superior to the medications described for the patient population at the end of life. A sound understanding of pharmacotherapy for pain treatment allows the palliative care/hospice team to create a comprehensive plan of care as well as recognize and assess medication related adverse effects, understand drug-drug and drug-disease interactions, and educate patients and caregivers regarding appropriate medication usage. Rational polypharmacy (combining drugs with different mechanisms of action to produce additive or synergistic effects and minimize adverse effects) is often necessary, but there is a high potential for drug interactions that require close monitoring.



• **Figure 82.2** Modification of the World Health Organization stepwise ladder approach to pain management may be utilized to avoid delay in adequate pain control for patients at the end of life. Advanced procedures can be used for pain at any level but should be strongly considered for patients with severe pain.

Non-opioid Analgesics

Acetaminophen

Acetaminophen has been determined to be one of the safest analgesics for long term use in the primary management of mild pain or as a supplement in the management of more intense pain syndromes. It is especially useful in the management of non-specific musculoskeletal pain or pain associated with osteoarthritis but should be considered an adjunct to any chronic pain regimen. It is often forgotten or overlooked when severe pain is being treated in terminally ill patients, but it can be quite effective as an adjuvant medication. It is important to consider acetaminophen's limited anti-inflammatory effect and its risk of hepatotoxicity. Reduced doses or avoidance of acetaminophen is recommended for patients with renal insufficiency or liver failure, particularly in individuals with significant alcohol use.[96]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are useful in treating moderate to severe pain in many pain conditions mediated by inflammation. These medications are useful either alone or as adjuncts to opioid analgesic therapy and may be effective for pain of somatic origin such as bone, muscle, and skin in both cancer and non-cancer disease states.[97] These agents cause minimal nausea, constipation, sedation, or effects on mental function. However, there is evidence that their use can impair short term memory in older patients.[97] Adding NSAIDs to an opioid regimen may allow a reduced opioid dose when sedation, obtundation, confusion, dizziness, or other central nervous system effects of opioid analgesic therapy alone become problematic.[97] Extended-release formulations and alternative routes of administration of NSAIDs are available and can be used to increase compliance and adherence.[93] As with acetaminophen, decreased renal function and liver failure are relative contraindications for NSAID use. Patients with cardiovascular risk, platelet dysfunction, or other potential bleeding disorders are more definite contraindications to using NSAIDs. Gastrointestinal complications may be mitigated by the use of cyclooxygenase-2 (COX-2) selective NSAIDs such as celecoxib and low dose meloxicam or coadministration of proton pump inhibitors.[93,98] However, prolonged use of NSAID therapy should still be used with caution in high risk palliative care patients.

Naltrexone

Naltrexone is an antagonist at μ-opioid receptors that is currently approved for use in opioid and alcohol dependence but has shown potential as a non-opioid therapy for chronic pain and palliative care.[99] Low dose naltrexone exhibits pharmacologic activity against central, neuropathic, and inflammatory pain and appears to modulate or enhance endogenous opioid production without significant adverse effects. Further clinical research is required to validate efficacy.

Opioid Analgesics

Opioid analgesics are the most useful agents for the treatment of pain associated with advanced disease from chronic end stage illnesses and cancer.[100] The opioids used most commonly in palliative care are morphine, hydromorphone, fentanyl, oxycodone, and methadone. The only absolute contraindication to the use of an opioid is a history of a hypersensitivity reaction (e.g. rash, wheezing, and edema). Allergic reactions are almost exclusively limited to the morphine derivatives, and the prevalence of true allergic reactions to synthetic opioids is much lower. Opioid analgesics may accumulate toxic metabolites over time, especially when drug clearance and elimination decrease as disease progresses and organ function deteriorates.[101] Use of meperidine is specifically discouraged for repeated dosing over time because of its neurotoxic metabolite, normeperidine.[102] The mixed agonist-antagonist agents, typified by butorphanol, nalbuphine, and pentazocine, are not recommended for the treatment of pain in patients with advanced disease. They have limited efficacy, and their use may cause an acute abstinence syndrome in patients using pure agonist opioids.[103] For further information on opioids and chronic opioid therapy, see Chapter 48.

Morphine

Morphine, the prototype agonist, is considered the gold standard of opioid analgesics and is used as a measure for dose equivalence.[104] It is available in oral, rectal, intravenous, and spinal preparations. Although some patients cannot tolerate morphine because of pruritus, headache, dysphoria, or other adverse effects, common initial dosing effects, such as sedation and nausea, often resolve within a few days.[105] It is best to anticipate these adverse effects, especially constipation, nausea, and sedation, and prevent or treat appropriately. Morphine-3-glucuronide, a metabolite of morphine, may contribute to myoclonus, seizures, and hyperalgesia, particularly when patients cannot clear the metabolite because of renal impairment.[106] Side effects and metabolite effects can be differentiated over time. Side effects generally occur soon after the drug is absorbed, whereas metabolite effects are generally delayed by several days. Morphine's bitter taste may be prohibitive, especially if "immediate release" tablets are left in the mouth to dissolve. In this case, several options are available. One available type of long-acting morphine comes in a capsule that can be opened, releasing small pellets that can be mixed in applesauce or other soft food.[107] Oral morphine solution can be swallowed, or small volumes of a concentrated solution can be placed in the mouth of patients whose voluntary swallowing capabilities are significantly limited.[107]

Oxycodone

Oxycodone is a synthetic opioid that is only available as an oral formulation. Immediate-release (alone or with acetaminophen) and extended-release (OxyContin^{R}) are found in tablets and liquid forms. It is nearly as lipid soluble as morphine but has better oral absorption.[108] Side effects appear to be similar to those experienced with morphine, but one study comparing the two formulations in patients with advanced cancer found that oxycodone was less likely to cause nausea and vomiting.[109]

Hydromorphone

Hydromorphone is a synthetic opioid that can be a useful alternative to morphine in patients at the end of life. It is available in oral tablets, liquids, suppositories, parenteral, and spinal formulations. Extended-release formulation (Exalgo^{R}) is only available in oral tablet form at this time. As a synthetic opioid, hydromorphone can be useful if there is inadequate pain control or when patients experience true allergic responses to morphine or intolerable side effects occur. The metabolite hydromorphone-3-glucuronide may lead to similar opioid neurotoxicity seen with morphine metabolites: myoclonus, hyperalgesia, and seizures, especially in patients with renal dysfunction.[110]

Fentanyl

Fentanyl is a potent lipophilic opioid that can be administered via several different routes, including intravenous, spinal, transdermal, and transmucosal. Because of its potency, dosing is

conducted in micrograms. Careful fentanyl dosing is particularly important in older patients; a study of transdermal fentanyl in postoperative patients found that absorption was significantly delayed in men 64 to 82 years old compared with men 25 to 38 years old.[111] Opioid naïve patients should begin with titrated immediate-release opioids to establish the needed 24 h dose of opioid before determining that the lowest available dose, currently a 12.5 mcg/h patch, can be tolerated. Oral transmucosal fentanyl citrate is composed of fentanyl on an oral applicator to provide rapid absorption of the drug within minutes that can be effective for rapid episodic pain relief such as painful dressing changes. This formulation of fentanyl is particularly useful for breakthrough pain in patients without parenteral access, as demonstrated in the first clinical report of its use for this indication in a terminally ill patient.[111]

Methadone

Methadone has several characteristics that make it useful in the management of severe, chronic pain.[112] Methadone is available in oral and intravenous formulation and has a half-life of 24–36 h with a much longer terminal half-life, allowing for prolonged dosing intervals. However, the analgesic half-life of methadone is often much shorter. Methadone is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, which may be of particular benefit in neuropathic pain.[113] Methadone is much less costly than comparable doses of proprietary continuous-release formulations, making it potentially more available for patients without sufficient financial resources for more expensive drugs.

Despite these advantages, much is unknown about the appropriate dosing ratio between methadone and morphine, as well as the safest and most effective time course for conversion from another opioid to methadone.[113] Current data suggest that the dose ratio increases as the previous dose of oral opioid equivalents increases, and although the long half-life is an advantage, it also increases the potential for drug accumulation prior to achieving steady state blood levels.[113] There may be a risk of over-sedation and respiratory depression after two to five days of treatment with methadone. Close monitoring of these potentially adverse or even life-threatening effects is required. Data suggest that methadone can also lead to life-threatening QT interval prolongation.[112] Therefore patients on methadone therapy should have interval QT screening before and during treatment.[112]

Patients currently receiving methadone as part of a maintenance program for addiction therapy often develop cross-tolerance to opioids and require higher doses than opioid naïve patients.[114] Prescribing methadone for this specific diagnosis requires a special license. In the United States, so prescriptions for methadone to treat pain must specify "for pain."

Buprenorphine

Buprenorphine is a synthetic mixed agonist-antagonist that is available in intravenous, sublingual, and transdermal formulations. Transdermal buprenorphine has been used similarly to methadone in the treatment of opioid addiction but has also been shown to provide effective analgesia for moderate to severe chronic pain as well as cancer pain.[115] Although the effectiveness of this opioid therapy has not been studied compared to other standard opioid analgesics, it has a unique pharmacologic profile that distinguishes its potential use for specific patients. Buprenorphine carries a ceiling effect for respiratory depression when used with or without other central nervous system depressants, which may provide a safer analgesic option for patients with end stage respiratory disease. Primary hepatic metabolism and elimination allow its use without dose reduction in patients with renal dysfunction. It has also been shown to have benefits in improving neuropathic pain symptoms.[116] Although buprenorphine may provide effective analgesia for opioid naïve patients, it must be used in caution with opioid tolerant patients in whom it can precipitate withdrawal symptoms.

Tapentadol

Tapentadol is a newer opioid that acts as a weak opioid agonist and a noradrenaline reuptake inhibitor. This drug is available in the immediate- and extended-release formulation and has no significant active metabolites. The gastrointestinal related side effect profile is decreased compared to strong opioids, and reviews have shown similar effective analgesia.[117] Therefore this may be an alternative option for patients that have failed standard opioid therapy because of inadequate pain control or intolerable side effects.

Routes of Administration of Opioids

The oral route is generally preferred when patients are capable and enteral absorption is not problematic. Enteral feeding tubes can also be used when patients can no longer swallow. In the palliative care setting, alternative routes of administration must be available for patients who can no longer swallow or when other comorbidities preclude the oral route.[118] These include transdermal, transmucosal, rectal, vaginal, topical, and neuraxial (epidural, intrathecal). In a study of cancer patients at four weeks, one week, and 24 h before death, more than half of the patients required more than one route of opioid administration. As patients approached death and oral use diminished, the use of intermittent subcutaneous injections and intravenous or subcutaneous infusions increased.[17] Therefore in caring for patients near the end of life, it is essential to identify alternatives to oral administration that can be used if necessary.

Some opioids have available commercial preparations in the form of suppositories, compounded suppositories, or microenemas that can be used to deliver the drug directly to the rectum or stoma. Sustained-release morphine tablets have been used rectally, with documented efficacy and safety as compared to oral administration.[119] The rectum, stoma, or vagina can also be used to deliver medication. However, the use of these routes may be hindered by the presence of fecal contents, mucosal dryness, thrombocytopenia, or painful lesions. Vaginal administration may require a tampon covered with a condom or an inflated urinary catheter balloon to prevent early discharge of the drug since the vagina has no sphincter. Although useful, the rectal or vaginal routes may be unacceptable to many patients and their caregivers, especially when the patient is obtunded or unable to assist. Nebulization is an alternative route for opioid administration that has been utilized for the relief of dyspnea but continues to be studied for analgesic efficacy. Nebulized morphine, fentanyl, and hydromorphone have been found to decrease respiratory and heart rate and increase oxygen saturation with only mild or moderate adverse effects of drowsiness, cough, bitter taste, or claustrophobia because of nebulizer mask.[120]

Transdermal fentanyl or buprenorphine are available in adhesive patch form. This route of administration is particularly useful when patients cannot swallow, do not remember to take medications or experience adverse effects from other opioids. Patients should be monitored by a responsible caregiver for the first 24–48 h of therapy until steady state blood levels are reached. The transdermal route of administration may not be appropriate

for patients with fever, diaphoresis, cachexia, morbid obesity, and ascites, all of which may significantly affect the absorption, blood levels, and clinical effects of the drug.[111] Some patients experience reduced analgesic effects within 48 h of applying a new patch. The option of more frequent (every 48 h) patch changes must be weighed against whether a higher dose can be tolerated with increased duration of effect. Patches are not suitable for severe uncontrolled pain because of the inability of rapid titration. Under most circumstances, breakthrough pain medications should be available to patients using any continuous-release opioids, such as transdermal patches.

Although most patients do well on the oral or transdermal route of opioid administration, some may require temporary or ongoing administration through a parenteral route.[57,58] Parenteral administration in palliative care is usually limited to subcutaneous and intravenous delivery because repeated intramuscular opioid delivery is excessively noxious. The most common indications for a parenteral infusion are bowel obstruction or malabsorption, severe stomatitis, intractable nausea and vomiting, and dysphagia.[57,58] A parenteral opioid infusion also is considered for patients with rapidly escalating and unstable pain or those with frequent and severe episodes of breakthrough pain. In these situations, the use of patient-controlled analgesia in combination with the continuous parenteral infusion helps ensure more effective pain relief.

The intravenous route provides rapid and continuous drug delivery but requires vascular access that is costly and may not be easily obtained or maintained in a home or long term care setting. Continuous infusions are usually only considered in patients who have an indwelling central venous port or other long term central venous device. However, in most cases, a continuous subcutaneous infusion can accomplish the goals of therapy without the need for intravenous access. Subcutaneous bolus administration of opioids has a slower onset and lower peak effect when compared with intravenous bolus. However, the subcutaneous route of administration is an inexpensive and effective method to achieve adequate pain control with minimal side effects and requiring minimal training for use in the home setting.[121]

Neuraxial routes, including epidural or intrathecal delivery, may allow administration of drugs, such as opioids, local anesthetics, and α-adrenergic agonists. However, this method for medication delivery requires complex placement and equipment by healthcare professionals with potentially greater caregiver burden. The risk of infection and other complications, along with higher initiation and maintenance costs, are significant concerns when considering intraspinal delivery systems. Patient selection should be based on greater than six months' life expectancy for implanted programmable pumps and adequate organizational infrastructure to manage these devices.

Discharge planning for patients receiving parenteral therapy is more complex and requires a team approach, with good communication between the hospital and community. A discharge planner can facilitate referral to home care agencies such as a home infusion company and identify constraints with insurance or drug availability. Operation of the infusion device may be accomplished by a home infusion care nurse or families that have been trained. All patients and their families who are receiving a parenteral infusion at home must have a 24 h resource person available to them to troubleshoot the system. The most common error encountered in a continuous infusion at home using a computerized pump is incorrect programming, leading to an inadvertent overdosing or under-dosing of the patient. Patients receiving parenteral therapy should be adequately monitored for signs of increasing pain or the occurrence of side effects such as increasing sedation, nausea, or vomiting.

Adjuvant Therapies

The term *adjuvant analgesics* is often used synonymously with *co-analgesics* and *pain-modifying drugs*. A wide variety of non-opioid medications from several pharmacologic classes have been demonstrated to reduce pain caused by various pathologic conditions or modify the ongoing disease process in a way that specifically reduces pain. Under most circumstances, these drugs are indicated for the treatment of severe neuropathic pain or bone pain, and opioid analgesics are used concurrently to provide adequate pain relief. Typical adjuvants include tricyclic anti-depressants, serotonin-norepinephrine reuptake inhibitor anti-depressants, anti-convulsants, corticosteroids, and other disease-modifying drugs, such as bisphosphonates for metastatic bone pain. For more information on adjuvant analgesics, see Chapters 53–57.

Anti-depressants

The analgesic effect of tricyclic anti-depressants appears to be related to inhibition of norepinephrine and serotonin reuptake, making these neurotransmitters more available within central nervous system pain inhibitory pathways. There are many significant, controlled clinical trials for several pain conditions, and guidelines list tricyclic anti-depressants as one of the first line therapies for neuropathic pain.[122] Analgesic doses of anti-depressants are generally much lower than the effective dose for the treatment of depression. Although the significant side effects of tricyclic anti-depressants require careful titration and monitoring in elderly and palliative care populations, their sleep-enhancing and mood-elevating effects may be beneficial enough to outweigh their disadvantages.[123] The newer mixed selective serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine may offer some of the advantages of tricyclic anti-depressants without the anticholinergic side effects.[124]

Anti-convulsants

The older anti-convulsants, such as carbamazepine and clonazepam, are recognized to relieve pain by blocking sodium channels.[123] These compounds are very useful in the treatment of certain types of neuropathic pain, especially pain with episodic, lancinating qualities such as trigeminal neuralgia. The mechanism of analgesic action of gabapentin and pregabalin is thought to result from calcium ion channel blockade.[125] Gabapentin has shown efficacy in the treatment of non-malignant neuropathic pain such as painful diabetic neuropathy, whereas pregabalin has been shown to be superior in managing neuropathic cancer and cancer treatment related pain.[126] Additional evidence supports the use of gabapentin in neuropathic pain syndromes seen in palliative care, such as thalamic pain, pain because of spinal cord injury, cancer pain, and restless legs syndrome, and HIV-associated sensory neuropathies.[127] Withdrawal from anti-convulsant medications, if indicated because of ineffectiveness or adverse effects, should be gradual to prevent possible seizures.[128]

Corticosteroids

Corticosteroids are particularly useful for neuropathic, visceral, and bone pain syndromes in patients with far advanced disease, including plexopathies and pain associated with stretching of the liver capsule as a result of metastases.[129,130] Dexamethasone

produces the least amount of mineralocorticoid effect, making it the least toxic choice. Dexamethasone is available in oral, intravenous, subcutaneous, and epidural formulations that can be administered once daily because of the long half-life of this drug. Usually, divided doses are used to mitigate high dose toxic effects, such as psychosis and severe blood sugar abnormalities in diabetic patients. High dose corticosteroids may be given with severe pain crises, similar to the doses used in acute neurologic emergencies. Intravenous bolus doses should be administered over several minutes to reduce untoward reactions, such as burning sensations. Intravenous doses should also be considered for patients on maintenance corticosteroid therapy that cannot maintain oral therapy as abrupt discontinuation can induce withdrawal symptoms.

Local Anesthetics

Local anesthetics are helpful in relieving neuropathic pain. They can be given orally, topically, intravenously, subcutaneously, or neuraxially.[131] Mexiletine (oral) has been reported to be useful when anti-convulsants and other adjuvant therapies have failed.[132] Electrocardiogram evaluation prior to initiation of therapy is recommended to assess for conduction blocks that can be exacerbated by local oral anesthetics. Local anesthetic gels and patches have been used to prevent pain associated with needlesticks, minor procedures and reduce the pain of postherpetic neuralgia.[133] Intravenous lidocaine in a continuous infusion has been reported to reduce intractable neuropathic pain in inpatient palliative care and home hospice settings.[134] Epidural or intrathecal lidocaine or bupivacaine delivered in combination with an opioid can provide a superior reduction of neuropathic pain.[135]

Bisphosphonates

Bisphosphonates inhibit osteoclast-mediated bone resorption and alleviate pain related to metastatic bone disease and multiple myeloma. Bisphosphonates can be used to reduce the incidence of pathologic fractures and to treat tumor-related hypercalcemia.[136] Zoledronic acid has demonstrated improved safety and efficacy than pamidronate, specifically in patients with breast cancer and multiple myeloma.[137] Similarly, there appears to be more sustained pain relief with zoledronic acid compared with other bisphosphonates in patients with metastatic prostate cancer.[138] Clinical trials in patients with lung and renal cell carcinoma have also shown therapeutic benefit from regular infusions of zoledronic acid.[139]

Palliative Chemotherapy and Radiation Therapy

Palliative chemotherapy is the use of antitumor therapy to relieve the symptoms that are associated with malignancy. Considering patient goals, performance status, tumor sensitivity, and potential toxicities, chemotherapy can be utilized to optimize symptom control and quality of life even though it may not improve survival.[118] Radiation therapy is also a highly useful adjunct to control pain from bone metastasis and pressure-inducing and ulcerative malignancies. Single-fraction and hypofractionated regimens are proving to be effective in very sick patients and those with limited life expectancy in whom the costs of multiple treatment sessions are untenable.[140] These therapies are often underused in hospice or palliative care and should be considered for any patient with a life expectancy of more than a few weeks.[141]

Therapy for Intractable Pain

The use of ketamine and dexmedetomidine has gradually increased in the management of intractable pain in cancer patients and terminally ill patients. Ketamine is a potent NMDA-receptor-channel blocker available for administration in oral, sublingual, intranasal, topical, subcutaneous, and intravenous formulations. It is used in subanesthetic doses for both pain and mood disorders without causing respiratory or cardiovascular depression.[142] Ketamine may also be helpful in the reduction of opioid consumption and tolerance. It has been found to be more effective in neuropathic pain, ischemic pain, and regional pain syndromes.[143] Dexmedetomidine is a selective alpha-2 adrenergic agonist that is administered intravenously that can produce sedation and analgesia but does not cause respiratory depression. Dexmedetomidine has also been shown to be potentially useful for severe or refractory pain, delirium, and opioid induced hyperalgesia.[144] The use of ketamine or dexmedetomidine infusions in a non-intensive care hospital care setting may allow for a window of time to achieve optimal pain control with primary regimen escalation or to allow patients to achieve other goals in their terminal phase. Ultimately if pain cannot be controlled, there is an option for palliative sedation. Palliative sedation is the infusion of medication to lower the level of consciousness of a patient to limit the awareness of suffering that a patient finds intolerable and intractable. Though this modality has met resistance in the past, it has been through the scrutiny of both ethicists and judges coming out as an acceptable practice for the properly selected patients. Studies have demonstrated that patients undergoing palliative sedation experience no life-shortening effect.[145]

Cannabis for End of Life Therapy

Cannabis in plant-based products has multiple components creating a synergistic entourage compared to synthetic cannabis products primarily used for medicinal formulations. Patients with advanced cancer using cannabis have reported improvements in pain, appetite, nausea, and overall general wellbeing.[146] Many providers have changing attitudes of cannabinoid use that appear to be in part related to legalization efforts. However, this acceptance has not translated into actual recommendation and prescription.[147] There remains a paucity of high quality evidence on using cannabinoids to treat cancer-related and terminal illness pain. Most studies clearly document potential adverse effects of dizziness, nausea, fatigue, somnolence, disorientation, drowsiness, and confusion.[126] These may be particularly important when considering the frailty, baseline symptoms, and other comorbidities of this patient population.

Beginning Therapy, Adding or Changing Drugs, and Breakthrough Pain

Initial analgesic therapy and dosing will depend on patient-specific medical, psychological, and social considerations and sound knowledge of pharmacotherapy. Frail patients and those with pain crises may require observation in a monitored setting to provide safe and effective relief within an acceptable time frame. Opioids should be initiated in immediate-release form in lower doses for opioid naïve patients because of significant inter- and intraindividual variation in clinical responses. Idiosyncratic responses may require trials of different agents to determine the most effective drug and route of delivery for any given patient.

Prompt reassessment within one or two days is essential so that adjustments can be made as soon as possible. Poor pain control after initiation of therapy may be because of inadequate dosing or end of dose failure. Titration and combination of drugs that may provide additive or synergistic effects should proceed along rational lines, based on the pharmacokinetics and monitored pharmacodynamics of the drugs. Patients continuing to take increasing doses of immediate-release medications as needed more than four times daily with inadequate pain control should be considered for additional extended-release opioid. This dose is determined by calculating the total daily dose of immediate-release medication used in a 24 h period and dividing it in half to approximate the extended-release dose to be administered twice daily. Transitory flares of pain, or breakthrough pain, may still occur both at rest and during movement. If breakthrough pain lasts longer than a few minutes, the patient may continue to take immediate-release opioid to provide relief.

For safety, a patient should reach a steady state on the current regimen before titration. Medications generally require four to five half-lives to reach a steady state, approximately 24 h for immediate-release opioids and two to three days for extended-release opioids. If adverse effects exceed the analgesic benefit of the drug, it may be converted to an equianalgesic dose of a different opioid. However, opioid rotation should not be the first option for patients experiencing mild side effects, as most of these will be time limited.[126] For patients with intolerable side effects, poor pain despite adequate titration, changes in the route of administration, change in end organ function, or unsafe drug interactions, rotation in opioids should be addressed. Because of incomplete cross-tolerance in transitioning opioid classes, consider reduction of the calculated dose by one-third to one-half and titrate upward based on pain scores.[118]

Minimizing and Managing Adverse Effects

There are a variety of adverse effects that drugs for pain can cause patients in palliative care. The normal side effects of pain relief medications are often exacerbated by changes in metabolism caused by end stage disease, polypharmacy associated with advanced age, and other factors. Following are some of the more common adverse effects and an overview of possible approaches to preventing or alleviating them.

Constipation

Opioid induced constipation is any change from baseline bowel habits when initiating opioid therapy.[126] A prophylactic bowel regimen with stool softeners and/or bowel stimulants should always be started when commencing opioid analgesic therapy. Bulking agents, such as psyllium, should be avoided because these tend to increase desiccation time in the large bowel, and debilitated patients can rarely take in sufficient fluid to facilitate their action. If over-the-counter medications are ineffective at creating regular laxation, prescription therapies are indicated. When traditional regimens have failed to bring about the desired effect, using a peripherally acting μ-opioid receptor antagonist such as methylnaltrexone can be useful. Multiple drugs in this class have been formulated to target opioid induced constipation, and because they do not enter the central nervous system, there are no symptoms of opioid withdrawal or increased pain. Pure opioid antagonists, which are generally used to treat acute overdose, can be used in selected cases to prevent opioid induced bowel dysfunction.[148]

Sedation

Opioid induced neurotoxicity can include symptoms of delirium, tremor, myoclonus, and hallucinations that are associated with opioid therapy. In addition, sedation serves as a warning sign that occurs before respiratory depression. Excessive sedation may occur with initial doses of opioids, but if sedation continues to persist after the first few days and other correctable causes have been identified and treated, then dose reduction may be warranted. However, some studies have shown the use of psychostimulants to be beneficial in counteracting opioid induced sedation in cancer patients.[149] These medications include dextroamphetamine, methylphenidate, and modafinil.

Respiratory Depression

Respiratory depression is rarely a clinically significant problem for opioid tolerant patients who are in pain.[94] When respiratory depression occurs in a patient with advanced disease, the cause is usually multifactorial.[150,151] When depressed consciousness occurs along with decreased respiratory rate or hypoxemia and is associated with opioid use, slow, cautious titration of diluted naloxone can be administered every few minutes while providing respiratory support and supplemental oxygen. Excessive administration of naloxone may cause abrupt opioid reversal with pain and autonomic crisis.

Nausea and Vomiting

Nausea and, less commonly, vomiting may be adverse effects associated with opioids because of activation of the chemoreceptor trigger zone in the medulla, vestibular sensitivity, and delayed gastric emptying. Habituation usually occurs in most cases within several days.[118] In severe or persistent cases without other identifiable causes, antiemetic pharmacotherapy or consideration of transdermal route is indicated.[97]

Myoclonus

Myoclonic jerking can occur with high dose opioid therapy, particularly with morphine in the face of renal dysfunction because of metabolite accumulation.[118] Opioid rotation is warranted with additional consideration of benzodiazepines such as clonazepam, lorazepam, or Valium to treat distressing myoclonus.[94] High dose opioid infusions should be requested in preservative free solutions because of reported associated grand mal seizures.[152]

Pruritus

Pruritus because of histamine release can occur with most opioids, although it appears to be most common with morphine. Most antipruritic therapies cause sedation, which should be confirmed as an acceptable alternative by the patient. Antihistamines (such as diphenhydramine) are the most common first line approach to this opioid induced symptom. Ondansetron and pentazocine have also been reported to be effective in relieving opioid induced pruritus. However, both have some risk of recurrent opioid induced pruritis.[153]

Hyperalgesia

Opioid induced hyperalgesia is a paradoxical increase in sensitivity to painful stimuli with increasing doses of opioids. The escalation of pain or failure of analgesia following opioid titration may be because of high or rapidly increasing doses. Patients may experience pain in a different location or of a different quality. Managing opioid induced hyperalgesia entails opioid rotation or reduction and supplementation of non-opioid analgesics.[117]

Conclusion

Effective pain management in advanced medical illness and at the end of life is a critical component of quality medical care to ensure dignified, safe, and comfortable dying. To quote Sir William Osler, the "father of modern medicine," "The study of morbid anatomy combined with careful clinical observations has taught us to recognize our limitations and to accept the fact that a disease itself may be incurable and that the best we can do is to relieve symptoms and make the patient comfortable." A personalized and multifaceted approach to pain management to include nonpharmacologic and pharmacologic interventions for the patient continues to be warranted even at the end of life. Although the basic principles of pain management are the same whether the patient is being cared for in an acute care setting, their home, or a long term care facility, there is a major shift in responsibility for day-to-day pain management when the patient is cared for at home. Pain management in the home becomes a family experience with every aspect of care provided to the patient affecting the family system as a whole. Successful pain management at home depends on an informed and confident patient and caregiver with collaboration and effective communication between the family and designated primary individuals in their healthcare team. A system of continual assessment of patient and caregiver must be in place to ensure the effectiveness of pain relief measures and early identification of undue stress on the part of the caregiver.

Key Points

- Pain is a prevalent symptom at the end of life that is increasingly managed in the home environment.
- Assessment and management of pain becomes more complex at the end of life, becoming a family experience.
- Transitions and challenges to home pain management must be addressed to ensure adherence to a pain management plan, adequate analgesia, and decreased burden for caregivers.
- Tailoring a pain management regimen that fits the patient's and family caregiver's values, goals, and capabilities is important to maintain successful home care.
- Family and patient education in pain and symptom management, as well as ongoing support from competent pain practitioners, is essential.
- Clear, straightforward communication is a critical component of this education and support.
- Continuity of care and minimization of emergencies can be fostered through various tools of communication.
- Match the mechanism of pain with the class of drug whenever possible; initiate therapy and adjust the dose according to therapeutic response, side effects, and known pharmacokinetics of the drug.
- Nonpharmacologic approaches are effective pain management techniques at the end of life that can have positive impacts on the patient and their caregiver.
- Non-opioids should be considered in the treatment of mild to moderate pain of musculoskeletal origin.
- Opioid analgesic drugs are often necessary to relieve moderate to severe pain, and long-acting or sustained-release analgesic preparations should be used for continuous pain.
- Adjunctive drug therapies should be considered independently or concurrently with opioids, especially for neuropathic and bone pain.
- Anticipate, monitor, and treat breakthrough pain, changes nearing the end of life, and adverse effects of medications.
- Last, and perhaps most important, know your limitations. When a patient is not responding to therapy, be prepared to consult with someone who has more training, expertise, and experience. A team approach is often needed.

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PART 8

Research, Ethics, Healthcare Policy, and Future Directions in Pain Management

83

Clinical Trial Design Methodology and Data Analytic Strategies for Pain Outcome Studies

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It is traditionally held that the first comparative clinical trial was performed in 1747 by Dr. James Lind of the British Royal Navy to identify a treatment for scurvy. Lind evenly assigned 12 scurvy-afflicted sailors to receive cider, vitriol (a weak acid), vinegar, sea water, oranges, lemons, or nutmeg paste.[1] After six days, only the two sailors who had received oranges and lemons (and thus adequate amounts of vitamin C) had sufficiently recovered to return to duty. Two centuries later the advent of the pharmaceutical industry and the evolution of methodologic concepts led to the first controlled clinical trial in which patients were randomly assigned to different treatments. Performed in 1947–48, it was observed that the effects of streptomycin on pulmonary tuberculosis were significantly better than those of a placebo.[2,3]

Evidence-Based Medicine

In contrast to the previous common acceptance of the merit of individual medical or surgical practice—the proverbial "in my experience" (N of one), "in case after case, I have seen" (N of two), and "in my series" (N of three or more)—evidence-based medicine (EBM) acknowledges that simple intuition, unsystematic clinical experience, and a pathophysiologic rationale are inadequate bases for clinical decision making.[4] EBM stresses the critical examination of evidence from clinical research. EBM likewise offers a formal set of steps to complement medical training and "common sense" for clinicians to effectively interpret the results of clinical research ("how to read a paper") and to apply them in their practice. Lastly, EBM places a lower value on expert authority than does the traditional medical paradigm.[5–8]

EBM provides a process for evaluating evidence to inform clinical practice, which can be divided into five key steps. The first step is to **define a focused, clinically relevant question** with the goal of translating uncertainty into an answerable question. A useful structure for formulating an answerable clinical question is the mnemonic PICO:

P – Patient, Population, or Problem
I – Intervention
C – Comparison or Control
O – Outcome

The second step is to **search for evidence** by systematically retrieving the highest-quality information available to address the clinical question. The third step is to **critically appraise evidence** in terms of validity, clinical relevance, and applicability. The fourth step is to **apply the evidence in practice** to extrapolate scientific evidence and make a case-specific decision. The final step is an **evaluation of the clinical outcomes** and performance of the EBM-guided decision. EBM is not a linear process but rather an iterative, perpetually improving process made possible by continuous re-evaluation of the available evidence.[8,9]

Many systems for grading the level or quality of evidence and the strength of recommendations have been developed. Unfortunately, guideline developers worldwide have historically been inconsistent in how they rate the quality of evidence and grade the strength of recommendations, resulting in confusion among guideline users.[10]

While the GRADE system is not without limitations,[11] it has improved the standardization of EBM methods. GRADE defines and clearly delineates all the major domains that affect the reliability of research evidence, including the quantity, quality, consistency, and types of studies of the published evidence. This assessment results in one of four grades of evidence (high, moderate, low, or very low), which describes confidence in the estimated effect.[12,13] This certainty estimate may be rated down if there is a risk of bias, imprecision, inconsistency, indirectness, or publication bias.[14–18] Recommendations may also be assigned based on the evidence grade, an estimate of net benefit relative to harm, and other factors, including costs and burdens.[10,19,20] In GRADE, recommendations are graded as strong or weak, although groups implementing GRADE have used other categories (e.g. conditional instead of weak or an additional moderate category).

In some situations with GRADE, a moderate or strong recommendation might be justified, even when the evidence is of a low or very low quality. For example, a guideline found evidence for pulsed radiofrequency treatment of the dorsal root ganglion in the treatment of postherpetic neuralgia to be very low. However, the recommendation was graded moderately strong based on potential benefit relative to harm, as well as other considerations, including that the intervention is considered easy to perform and safe.[21] The terminology and development of practice recommendations are discussed later in this chapter.

Since the term was coined about 30 years ago,[22] EBM has progressed from a novel concept to a buzzword to a mantra.[23]

EBM is often misconstrued as being only about randomized clinical trials (RCTs). However, this is an oversimplification. In reality, EBM has always emphasized the importance of considering the best available evidence, which can include observational studies.[24]

The Spectrum of Outcomes Research

The appraisal of a new or existing treatment modality, including pain management, involves three steps.[25–29] These steps are ideally, but not always, undertaken sequentially.

1. **Efficacy**, or whether a treatment achieves its intended clinical benefits ("Can it work?"), is demonstrated under "optimal" circumstances in highly controlled settings with carefully selected patients, typically in an RCT.
2. The **effectiveness**, or whether these benefits are also seen under more ordinary or "naturalistic" circumstances, is assessed ("Does it work?"), often by way of an analytic cohort study, although RCTs can also be designed to evaluate effectiveness.
3. The **efficiency or cost effectiveness** (the health status improvement realized for a given amount of resources expended) can be determined via a healthcare economic evaluation ("Is it worth it?"). An economic evaluation can also provide crucial insight into the value of providing a healthcare intervention to a specific population (Figure 83.1).[30]

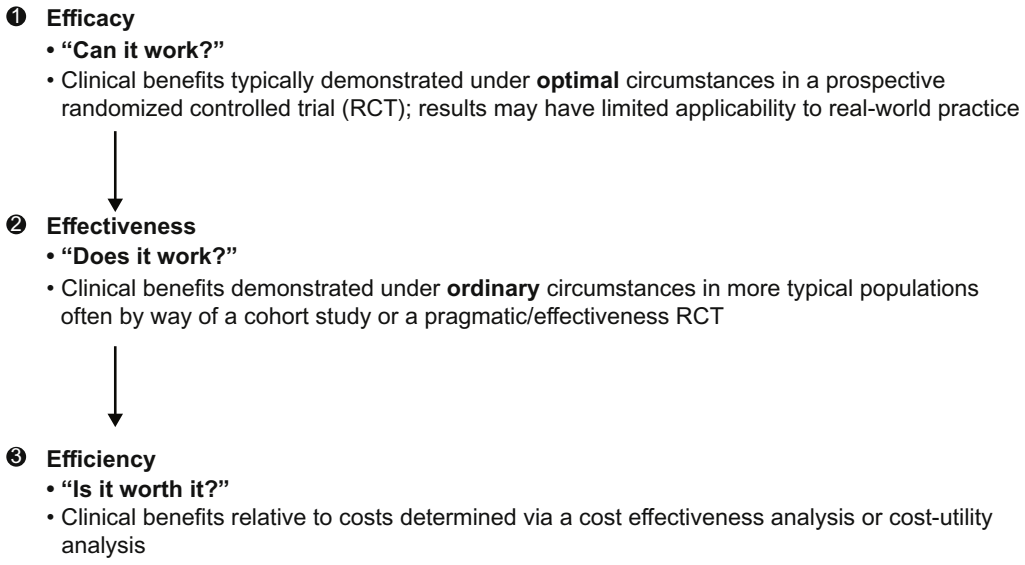
Importantly, for an intervention to be cost effective, it must first be shown to be effective. For example, routine imaging for low back pain (LBP) in the absence of "red flags" is associated with no benefit in pain or function compared to the usual care without routine imaging.[31] Therefore even though lumbar x-rays are relatively inexpensive, routine imaging cannot be cost effective. On the contrary, interventions associated with relatively high up-front costs can still be cost effective if the clinical benefits are substantial or the up-front costs are offset by decreased downstream costs. An example of such an intervention is the STarT Back screening tool, which stratifies patients based on the prognosis of LBP (low, medium, or high risk). At 12 months, compared with the non-stratified current best practice, STarT Back screening and treatment targeting was associated with a mean increase in general health benefits (0.039 additional QALYs) achieved with cost savings (£240.01–274,40), as well as fewer days off work.[32]

Experimental Versus Observational Study Designs

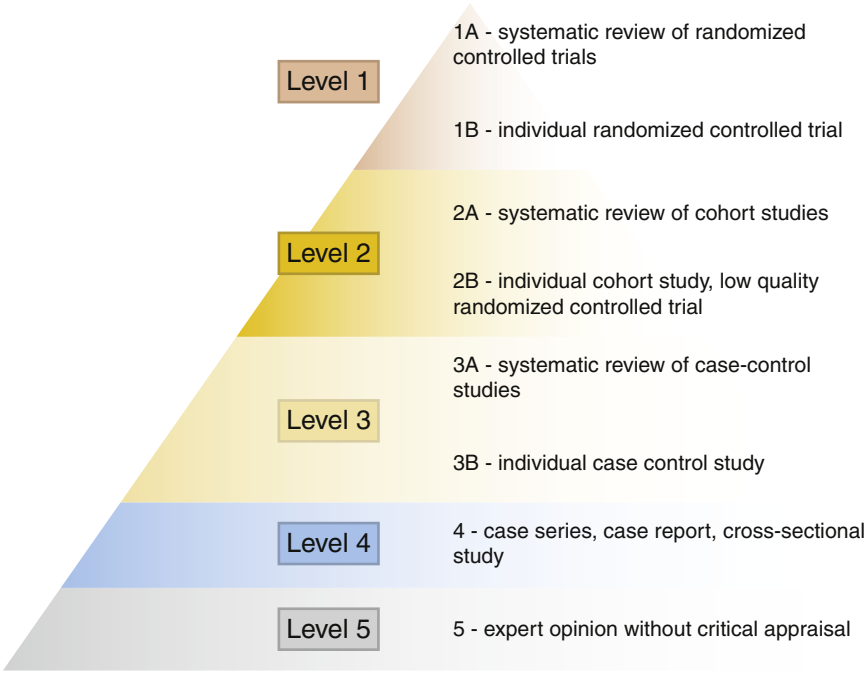
An RCT has been viewed by many clinician scientists (not to mention journal editors and reviewers) as the de facto "gold standard" of clinical trial design for evaluating the *efficacy* and safety of a treatment or intervention.[33] However, while a well-conducted RCT generally provides more valid (true) results than other study designs, there are several other study designs, which may on a situational basis, be more appropriate to apply in conducting human research.[34] For example, for evaluating harms, it may be unethical to randomize patients, or for rare or long-term harms, adequately powered RCTs may not be feasible.[35] The hypothesis posed dictates the study design that is the most appropriate. Different study designs were associated with ascending levels of strength (Figure83.2). Key characteristics that increase the strength of evidence are randomization, the presence of a control group, patient and investigator/provider blinding, low attrition, and control for known confounders.[36–39]

The array of quantitative study designs was classified as either experimental or observational. In an experimental trial, also called an interventional or controlled trial, the allocation of clinical interventions was determined by the investigators. This is not the case for observational studies, which are further divided into descriptive and analytic categories (Figure 83.3). A descriptive study focuses on describing a population, whereas an analytic study is characterized by the performance of the analysis involving a comparison group. Different study types are also distinguished by the timing of the data collection, which can be described as prospective or retrospective.[33,40–47]

Another distinction between the different study types lies in the tension and trade-offs between internal and external validity. Internal validity concerns include incomplete identification of and adjustment for confounders, misclassified variables, and selection bias, and require tight controls. External validity concerns include



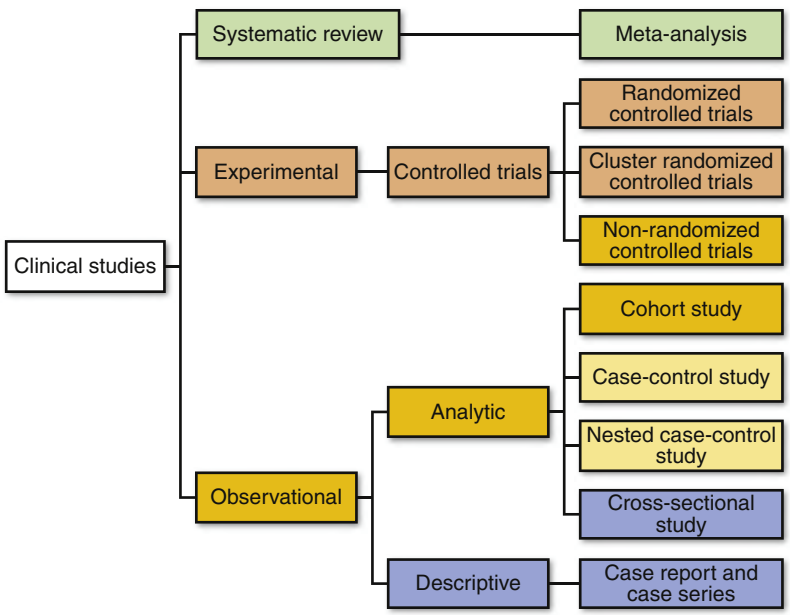
• **Figure 83.1** The appraisal of a new or existing treatment modality, including for pain management, involves three steps.



• **Figure 83.2** Levels of evidence based medicine.

the evaluation of selected populations, data handling, and timeliness.[48] External validity (generalizability or applicability) is separate from risk of bias but is also critical for interpreting research evidence. Studies may be at a low risk of bias and therefore valid (i.e. give true results) but only apply to very specific situations (i.e. have limited external validity). Therefore it is important to consider whether the study evaluates effectiveness or the extent to which a treatment works on average patients in everyday settings, as compared to efficacy, that is, the extent to which a treatment works in highly selected patients in tightly controlled settings.[49]

Observational studies can complement findings from often smaller scale RCTs by assessing treatment *effectiveness* in patients in a more realistic, natural clinical practice.[50] However, it is important to note that a randomized trial is not necessarily an efficacy study, nor is an observational study necessarily an effectiveness study. Rather, the aspects that determine whether a study is an efficacy or effectiveness study include the methods used to ensure that a study evaluates more representative populations, interventions, and comparisons; evaluation of patient-centered outcomes; and being conducted in settings typically encountered in clinical practice.[49]



• **Figure 83.3** Classification of clinical study designs.

Case Report and Case Series

A case report is useful, for sharing with the medical community, novel, rare, or atypical features identified in medical practice in an individual patient. It has historical significance as a type of clinical study that dates back by millennia.[51] However, since the mid-20th century, it has waned in terms of importance, in favor of more rigorous, statistically, methodologically relevant study designs.[52] Nonetheless, publication guidelines such as Consensus-based Clinical Case Reporting Guideline Development have been developed by international groups of experts to promote the accuracy, transparency, and usefulness of case reports.[53]

Currently, the case report remains a useful educational tool to generate new investigational questions and support learning methods rooted in critical thinking and problem solving. Case reports are also useful in pharmacovigilance because they facilitate sharing rare, unexpected, or long term adverse effects that may have gone undetected during clinical trials. Case reports contributed to the evidence that led to 18 of 22 drugs being withdrawn from the Spanish market between 1990 and 1999.[54,55] Important limitations remain, namely the lack of controls, uncertainty of a follow up, and the fact that it is difficult to generalize findings from a single patient.[56]

A case series can help address some of these concerns by increasing the sample size. A case series describes the medical outcomes of a group of patients with a particular disease or disease-related outcome, often over time. As with a case report, a case series comes with the primary limitation of the lack of a control group and potential sampling bias. Risk ratios cannot be calculated based on such evidence.[57]

An example of a case report, which represented the first reported occurrence of such an event, describes a patient who experienced an extremely rare and unpredictable thalamic stroke resulting in the disappearance of a pre-existing chronic pain condition,[58] following which the patient's chronic LBP completely disappeared. Such unique cases may provide insight into neuromodulation, neuroplasticity, and brain stimulation.[58]

Cross-Sectional Study

A cross-sectional study determines the prevalence (i.e. the existing presence) of a disease at a given point or period in time. If a sample is randomly chosen, such a frequency survey provides a valid "snapshot" of the characteristics of the source population. It can provide an estimate of the magnitude of a problem and thus the significance and rationale for further investigation. Of note, a cross-sectional study's measurements are taken at a single point in time, whereas longitudinal studies conduct several observations over time.[59] A cross-sectional study cannot assess possible causality between a predictor variable (e.g. sex and socioeconomic status) and an outcome variable (e.g. pain intensity). While a cross-sectional study cannot assess the comparative outcomes (benefits and risks) of an intervention, the findings of a cross-sectional study can generate hypotheses for further studies.[40–44,60,61]

For instance, a cross-sectional study aiming to investigate the frequency and features of painful diabetic polyneuropathy enrolled 816 patients attending hospital diabetic outpatient clinics.[62] Diabetic polyneuropathy was diagnosed in 36% of patients, strongly correlating with male sex, age, and severity of diabetes. A subset of these patients, 2.5% of the study population, with pure small-fiber polyneuropathy, was found to be unrelated to either the demographic variables or the severity of diabetes. On the contrary, painful polyneuropathy was correlated with the female sex and was diagnosed in 13% of the study population.[62] As discussed, cross-sectional studies cannot determine causality. However, demonstrating that this form of neuropathic pain correlates with sex offers insights that may contribute to improving pain management. Cross-sectional studies can be used to observe or compare individuals and groups. For example, a cross-sectional study examining social health determinants in patients following total knee arthroplasty divided their participants into two groups based on whether they had chronic postsurgical pain. This allowed them the investigators to see that patients with a lower educational level had a three-fold higher association with chronic post-surgical pain.[63]

Case-Control Study

A case-control study aimed to determine the relationship between a single outcome (disease) and one or more previous possible contributing factors (exposures). Case-control studies look or work backward, starting with the identified outcome or disease (exposure ß disease). Case-control studies are retrospective, relying upon existing data or recall of exposures, and are therefore generally less time consuming and less costly to perform than studies using a prospective design. This study design is particularly suited to outcomes that are rare or have a protracted onset. Cases are patients with the outcome of interest, whereas controls are patients without the outcome of interest. The controls must be drawn from the same source population (study base) as the cases, such that the controls are comparable to the cases in all important respects except for the outcome of interest.[64] Thus controls must also be chosen independently of their exposure status.

Primary validity threats with a case-control study include selection bias (non-comparable controls without the disease) and recall bias (differential recollection of exposure among cases with the disease). Overmatching can also occur if the cases and controls are matched on a variable that is also associated with the exposure of interest. Thus if someone matches a factor that is affected by both exposure and a cause of disease, this will obscure disease association.[65]

Because cases and controls are selected for analysis based on the presence or absence of outcomes, there is no true denominator in a case-control study. Therefore the event rate, relative risk, and risk ratio cannot be calculated. Instead, the odds ratio (the ratio of the odds of exposure in the cases and the odds of exposure in the controls OR) is conventionally generated as a measure of the association between exposure and disease in a case-control study. When the outcomes occur at an infrequent rate, the odds ratio should approximate the relative risk.[40–44,66]

A case-control study was performed to quantify the degree of overlap between facial pain and pain experienced in other parts of the body.[67] Data were collected from participants in a large prospective study, including 424 cases of chronic facial pain and 912 controls. They reported pain at other locations in the body using a mailed questionnaire. The findings were that facial pain had the greatest overlap with headaches (OR = 14.2, 95% CI = 9.7–20.8), followed by neck pain (OR = 8.5, 95% CI = 6.5–11.0). For locations below the neck, the overlap decreased substantially (OR ≤ 4.4).[67] A limitation of this study was its reliance on self-reported symptoms.

Nested Case-Control Study

A nested case-control study is a case-control study in which the cases and controls are selected from members of an existing cohort.[68] The members of the base cohort are followed for a certain period until the specific outcome or end-point occurs.[42,69] The nested case-control design differs from the non-nested case-control design in that patients are selected from a well-defined cohort, for which data on all members can be obtained.[70] This design makes it easier to satisfy the fundamental assumption of the case-control study: cases and controls represent unselected samples from the same study base.[70] In addition, a nested case-control study can be designed to prevent attrition bias. If all data are collected prospectively before the outcome occurs, a nested case-control study is also unlikely to be affected by recall bias, even though the cohort does not need to be prospective.[41]

The following is an example of a nested case-control study designed as a follow up to a 5-year cohort study, aiming to determine how headache types and patterns over time can be associated with the risk of developing temporomandibular disorder (TMD).[71] The cohort study followed 2410 patients who were TMD-free at the beginning of the study. The ensuing nested case-control study matched the cohort of 248 incident TMD cases with 191 TMD-free controls. The findings showed that both headache prevalence and frequency increased among patients who developed TMD compared to controls. In particular, in terms of headache frequency, definite migraines among TMD cases increased tenfold,[71] suggesting the usefulness of future studies in investigating whether the treatment of migraines may reduce the risk of developing TMD.

Cohort Study

A cohort study aims to determine the relationship between a single contributing factor (exposure) and one or more possible outcomes (diseases). Cohort studies look forward starting with the identified exposure (exposure à diseases). Cohort studies are, by definition, longitudinal. However, data collection can be prospective, retrospective, or ambispective (utilizing both retrospective and prospective data from the same study population). The key design element is that all participants in a cohort study are outcome or disease-free prior to exposure (intervention) and at the outset of data collection. The outcome data are then sequentially collected.

Prospective and retrospective cohort studies may be less prone to recall bias than case-control studies but are subject to differential attrition bias, whereby participants in one group exit the study at a disproportionate rate. Cohort studies are also vulnerable to confounding by indication, a form of selection bias in which a variable is a risk factor for a disease among the non-exposed individuals and is associated with the exposure of interest in the population from which the cases are derived, without being an intermediate step in the causal pathway between the exposure and the disease (e.g. a marked increase in gastrointestinal bleeding in patients prescribed a nonsteroidal anti-inflammatory drug [NSAID] plus a proton-pump inhibitor versus only an NSAID).[72,73]

Prospective cohort studies are also typically more time consuming and costlier than case-control or other observational studies, especially for rare outcomes (diseases) and those with a protracted onset. The cohort study allows for direct estimation of the incidence (new event) rate, relative risk, and relative risk ratio.[40–44,74] Of note, an RCT is a type of prospective cohort study with random assignment to exposures (interventions).[33]

A prospective cohort study was undertaken to identify predictors of moderate to severe persistent postoperative pain (PPP) 6–12 months after total knee arthroplasty (TKA).[75] The study population consisted of 300 patients undergoing primary unilateral TKA. Prior to surgery, a wide array of data was collected from the patients, including clinical information, psychological variables, quantitative sensory testing, and blood samples for genotyping, in addition to information on surgical factors related to the operation and measurements of acute postoperative pain. Thereafter, 6–12 months after surgery, the patients completed follow up questionnaires with minimal loss of participation, keeping the attrition bias low. All of this information was then analyzed using multivariate logistic regression to identify the predictors of PPP. The prevalence of moderate to severe PPP, 6 and 12 months after surgery, was 21% and 16%, respectively. At six months, 66% of patients were correctly classified as having moderate to severe PPP using a combination of the following predictive variables: preoperative pain intensity, expected pain, trait anxiety, and temporal summation. At 12 months, the same first three predictors correctly classified 66% of the patients.[75]

Non-Randomized Controlled Trial

In a non-randomized controlled trial (NCT), assignment to treatment and control groups is performed by the investigators but not through a randomized process. In contrast to RCTs, an NCT lacks the critical component or randomization, making them more susceptible to biases and confounding factors.[47] An inherent shortcoming of NCT is that it is difficult to determine whether differences in outcomes between interventions are because of the interventions themselves or other confounding variables.

Despite this important shortcoming, an NCT may be helpful in some situations in which RCTs are not feasible because of high cost, ethical considerations, lack of participants willing to be randomized, or other factors.[76] NCTs can be useful for identifying potentially effective interventions that warrant an evaluation in RCTs. NCTs are sometimes included in meta-analyses and used to inform medical decision making, but research is needed to understand when NCTs are more likely to be reliable and when they are likely to be misleading.

One such experimental controlled trial that relied on a non-randomized design aimed to determine the benefit of a 10-week shoulder home-based exercise program (SHEP) in a group of elite wheelchair athletes. The participants were assigned to either the exercise or control group in a non-random, mixed-pair design, where each participant was matched to a control in terms of two variables: whether they used the wheelchair for daily activities or only for sports, and whether they experienced shoulder pain or not. This design allowed the researchers to compare the baseline and post-intervention changes more accurately, both in terms of shoulder pain and range of motion. The 10-week SHEP did not provide significantly different changes in either outcome between the experimental and control groups. The limitations relating to non-randomized allocation and small sample size apply when it comes to the interpretation of this study's results in the context of similar studies.[77]

Randomized Controlled Trial

An RCT is a type of controlled clinical trial based on participants being assigned to the possible exposures or interventions purely by play of chance ("flip of a coin") using tools such as

computer-generated randomization sequences.[33] When successfully implemented, random allocation produces two or more treatment groups that are free of selection and confounding bias by both known and unknown factors, assuming that the sample size is sufficiently large and randomization is carried out successfully.[78] When those involved in an RCT are blinded (masked) to the intervention each participant receives, allocation, treatment, and assessment biases are also reduced.[79] Thus when properly designed and performed, an RCT is more likely to have internal validity. It accurately and reliably measures what it is intended to be measured, that is, the relative benefits and harms of two or more interventions.

Patient blinding is a critical factor contributing to the high quality and internal validity of a well-designed experimental trial. Moreover, double-blinding is achieved when both the patient and the investigator (if it is impossible to blind the investigator, the outcome assessor, data collectors, or data analyst may be blinded) are blinded to the treatment allocation. Successful double-blinding helps prevent response bias, such as observer bias and confirmation bias, which can be caused by the experimenters or the participants being influenced by their expectations of the results. In the case of either pharmacologic or non-pharmacologic interventions for chronic pain, blinding is rarely reported and has often been found to fail, primarily because of the large treatment effect sizes and high rates of adverse effects.[80]

An example of an RCT trial on chronic LBP investigated whether adding an open-label placebo (OLP) to treatment as usual (TAU) could benefit patients.[81] There are ethical concerns surrounding the study of placebo effects because of the widespread belief that deception is required in order for the placebo effect to take place. In this study, 97 participants consented to take OLP for three weeks following TAU treatment. The consenting participants were randomized to TAU or OLP, and the treatment assignment was revealed to both the participants and investigators. Only registered nurses who completed the assessments were blinded. The findings showed that OLP enhanced pain reduction by approximately 30% of the baseline pain and disability ratings. More specifically, OLP provided a pain reduction of 1.49 points on a 0–10 scale of pain intensity, compared to a 0.24-point change provided by TAU alone.[81] This study has some important limitations, primarily in terms of reporting bias, because of the utilization of self-appraised outcomes combined with an open-label design. Additionally, the highly positive response to OLP may be explained by the encouraging educational information the participants were provided with placebo effects, combined with unconscious processes associated with physically opening pill bottles and taking pills. Expectations of pain relief may have encouraged participants to differentially interpret normal spontaneous fluctuations in pain. A double-blinded study design is important for reducing unwanted placebo effects related to expectations of benefits or harm (nocebo effects). An alternative strategy is the use of an active placebo, which produces side effects intended to persuade the patient that they are receiving the active compound.[82]

An enriched enrollment randomized withdrawal (EERW) trial is a variation of the traditional RCT that has been introduced for studying chronic pain, particularly pharmacologic therapies. The first step of an EERW is the enrichment phase, where only the patients who respond to the drug and tolerate the side effects will progress to the next phase. In the withdrawal phase, these patients are then assigned, in a double-blind, randomized manner, into a group that will continue taking the study drug, and the control group will be switched, through titration, to a placebo or another comparator.[83,84] The EERW design may be considered an extreme form of efficacy study since it is intentionally designed to evaluate a highly selected patient population known to respond to and tolerate the treatment of interest. Furthermore, EERW studies reflect a highly selected population and are not representative of clinical practice, as the response to the drug cannot be predicted, and treatment would not normally be interrupted in patients who respond well. Additionally, patients withdrawn from treatment following randomization may be aware that they are no longer receiving the study drug, which may cause performance bias by influencing their response to the placebo.[83] Therefore the interpretation and utility of EERW studies have been controversial.[85]

Cluster Randomized Controlled Trial

A cluster randomized trial (CRT) is a study design in which individuals are randomized into groups; the group as a whole is randomized, and not the individual. Physicians, group practices, health plans, or even geographic regions (counties or states) can be defined as clusters. In a CRT, all individuals within a given cluster are assigned to the same study arm.[86] The methodology of CRTs has been widely discussed.[87–89] In evaluating a therapy, unlike a standard (individually randomized) RCT, a CRT may be better suited at replicating conditions of actual use in clinical practice to produce more generalizable findings.[90]

CRT is often performed when individual randomization is not feasible. For example, if a clinician is implementing a new LBP evaluation and treatment study protocol, it would be challenging to randomize some patients in a clinic to one protocol and other patients to another protocol because there is a substantial amount of shared knowledge of the different protocols and overlap among clinic personnel. CRT can also offer cost and time efficiencies over individually randomized trials.[86]

However, compared with individually randomized trials, CRTs are more complex to design, require more participants to obtain equivalent statistical power, and require more complex analyses (e.g. adjustment for the intracluster correlation coefficient of the cluster randomization).[91–93] A CRT is also typically not blinded. Thus not surprisingly, the use of this trial design creates challenges that may undermine the validity of some findings.[92,94]

For example, a CRT investigated the benefits of a digital health psychological intervention (WebMAP) in comparison to usual care alone in children and adolescents with chronic pain.[95] The 143 participants were patients selected from eight different clinics. The clustered randomization design that stems from the clinics determines whether they would initiate the WebMAP intervention two, four, six, or eight months after study commencement. The findings showed that neither WebMAP nor usual care showed significant changes in pain related disability and pain intensity over time. However, youths in the WebMAP group perceived a significantly higher global improvement both post-treatment and at follow up ($p \leq 0.01$). Additionally, greater engagement with the WebMAP modules was associated with a significant reduction in both pain related disability and pain intensity.[95] The clustered design of this study was used to implement the intervention. However, possible limitations are the potential differences in the amount or type of care provided at each clinic under usual care control. Nonetheless, the WebMAP intervention was provided through mobile access and was consistent among the groups.

Meta-Analysis

A systematic review involves a detailed and comprehensive search strategy to identify and appraise all relevant studies on a particular topic. A meta-analysis may then be performed to combine and compare the results of multiple scientific studies using statistical techniques to synthesize data into a single estimate or summary effect size.[96] Moreover, when conducted rigorously, it may provide the strongest synthesis or summary of evidence. Meta-analyses typically feature data from published RCTs. However, they can also include non-randomized, observational, and even unpublished studies.

A conventional meta-analysis makes direct comparisons between trials in a pairwise manner. More recently, network meta-analysis has emerged, which incorporates evidence from indirect comparisons using logical inference (i.e. comparing A to C using studies that compare A to B and B to C). The first step of a systematic review is a specific and well-formulated hypothesis, followed by a thorough and extensive literature review. The inter-judge reliability of those involved in the review and selection of studies for inclusion is an important component of meta-analytic reports. The next step is to evaluate the quality and strength of evidence for each study, based on the robustness of the study design and minimization of bias. Pooling of studies in meta-analyses can be performed using a variety of statistical methods. This is discussed in the statistical section of this chapter.

Several forms of bias could arise in a meta-analysis. One of the most important is publication bias because studies with positive, statistically significant results are more likely to be published, promoted, and thus identified in literature searches. However, meta-analyses are also one of the ways that enable us to detect publication bias, which is not possible when looking at individual studies. The principal methods for detecting publication bias are typically based on the detection of small sample effects. This refers to the fact that the findings of larger studies are more precise and tend to cluster closer to the "true" point estimate, whereas smaller studies are less precise, with more variability in point estimates. "Small sample effects" refers to unbalanced estimates from studies with small sample sizes that can be a marker of publication bias. Small sample effects can be detected through graphical methods (funnel plots) or statistical methods (e.g. Egger test). Clinical heterogeneity is common among meta-analyses because confounding factors, uneven blinding, and other effect modifiers are inconsistent among studies.[97–100] This reinforces the importance of stringent inclusion criteria and quality assessment using available guidelines.[101]

Healthcare Economic Evaluation

Healthcare economic evaluation has matured considerably in the last three decades. However, despite its widespread promotion, many physicians and researchers remain reluctant to apply economic evaluation methods in their clinical decision making and clinical trials, including chronic pain treatment modalities.[102,103] Much of this reluctance has been attributed to physicians and their innate propensity to think more in terms of clinical effectiveness and advocacy at the individual patient level rather than on cost effectiveness at the population or policy level.[25,104]

Furthermore, as witnessed by the ongoing, intense United States healthcare reform debate, there is a strong unwillingness among Americans and their elected officials to consider whether an intervention may be cost effective, often because of fears of government-mandated rationing of care and geriatric discrimination. A provision of the American Recovery and Reinvestment Act of 2009 created and funded the Patient-Centered Outcomes Research Institute (PCORI) to undertake rigorous comparative effectiveness research. The Patient Protection and Affordable Care Act of 2010 specifically prohibited PCORI from undertaking any comparative cost effective analyses using cost per quality-adjusted life year (QALY) as a common metric.[105–107] Nevertheless, given the aging United States population, the associated increasing healthcare utilization but decreasing active workforce, and the unsustainable growing percentage of the United States gross domestic product devoted to healthcare, there is a clear and imminent need for valid healthcare economic evaluation data to establish healthcare funding priorities, including those for chronic pain treatment modalities.[25,108] Different countries develop their own guidelines. For example, in the United Kingdom, economic analysis is part of the National Institute for Health and Care Excellence (NICE) guidelines.[109]

Efforts to provide optimal care while controlling unnecessary or wasteful healthcare expenditures should focus on delivering "high value, cost-conscious healthcare."[110] Whether an intervention provides such a high value depends on assessing whether its health benefits justify its costs. There are three key concepts for understanding how to assess the value of healthcare interventions. First, assessing the benefits, harms, and costs of an intervention is essential to understand whether it provides good value. Second, assessing the cost of an intervention should include the cost of the intervention and any downstream costs that occur because the intervention was performed. Third, the incremental cost effectiveness ratio estimates the additional cost required to obtain additional health benefits and provides a key measure of the value of a healthcare intervention. In the United States, most decision makers consider interventions that cost less than $50,000 per QALY gained as highly cost effective.[110,111] The point at which an intervention is not cost effective varies, although many decision makers consider up to US$100,000 per QALY gained as reasonably cost effective.

Conventional economic evaluation techniques include cost-minimization analysis, cost-benefit analysis, and cost-utility analysis (including cost effectiveness analysis).[103,112–115] A cost-utility analysis is a type of cost effectiveness analysis that measures outcomes using quality-adjusted life years or other similar measures. Such full economic evaluations require that two or more therapeutic interventions be compared concerning both their costs and effects.[112,116] The six fundamental steps in undertaking a full economic evaluation include 1) identifying the perspective of the study, 2) identifying the alternatives that will be compared, 3) identifying the relevant costs and effects, 4) determining how to collect the cost and effect data, 5) determining how to perform calculations for cost and effect data, and 6) determining how to depict the results, draw comparisons, and make conclusions.[112,116,117]

With proper planning, a healthcare economic evaluation can be validated and reported alongside a clinical RCT.[25,118–122] However, given the logistical challenges of such a conjoint study,[121] researchers often combine previously published cost and clinical outcome data to create a decision analysis model.[25,123] The validity of such studies depends on how well the model simulates the key clinical issues and the reliability of the assumptions and parameters used to estimate the costs, outcomes, and utilities. Therefore sensitivity analyses are critical for understanding how conclusions

might change depending on the variability or uncertainty of the key parameters.

For example, decision analysis modeling demonstrated the cost effectiveness of adding non-pharmacologic interventions for chronic LBP to usual care.[124] The study population was divided into four groups depending on their pain impact: high, moderate, low, and none. A typical baseline mix of patients was constructed with 25% low impact, 35% moderate impact, and 40% high impact chronic pain. To calculate QALY gains, societal costs were measured based on non-pharmacologic intervention, back-related healthcare costs, and productivity losses caused by absenteeism. The most cost effective intervention to add to usual care was yoga, with a societal cost savings of $1773 associated with QALY gains of 0.048. Based on the generally accepted willingness-to-pay of $50,000/QALY, only traditional Chinese acupuncture was found to not be cost effective in complement with usual care, as it carried a societal cost of $302 and only gave QALY gains of 0.004.[124]

Methods for considering cost effectiveness when evaluating evidence are evolving. GRADE recommends that resource considerations, though not necessarily cost effectiveness analyses, be included in the evidence profiles and summary of findings tables. Because of variation across countries and over time, it is recommended that resource use (costs) be measured in natural units, such as the duration of inpatient hospital stay or the number of outpatient visits. The key considerations for making GRADE recommendations on economic evaluation are as follows: 1) identifying specific items of resource use that may differ between alternative interventions, which may be important to patients and decision makers; 2) finding evidence for the differences in resource use between the interventions being compared; 3) rating the confidence and quality of effect estimates using the same criteria as for the health outcomes; and 4) valuing the resource use for the specific interventions for which the recommendations are being made.[125]

Standards for Reporting Study Design and Findings

In 1858 Pasteur introduced the methods section of the scientific report, creating what is now known as the IMRAD format (Introduction, Materials and Methods, Results, and Discussion).[126,127] Not surprisingly, in the subsequent 150 years, as investigators have applied the above various basic study designs, there has been wide variability in their application and the content and organization of their published reports. In response, standards for reporting of study design and findings have been promulgated, several of which are applicable to acute and chronic pain management (Table 83.1). The Enhancing the Quality and Transparency of Health Research (EQUATOR) network was created to monitor and propagate the proper use of these guidelines,[128] and thus "to improve the quality of scientific publications by promoting transparent and accurate reporting of health research."[129] Furthermore, an increasing number of major (high impact) clinical and healthcare journals require or recommend adherence to the applicable set of such guidelines for submitted manuscripts.

TABLE 83.1 The Various Publication Guidelines

Acronym	Full Title of Guideline	Notes
EQUATOR	Enhancing the quality of and transparency of health research	http://www.equator-network.org/
CONSORT[a]	Consolidated standards of reporting trials[130]	http://www.consort-statement.org/
STROBE	Strengthening the reporting of observational studies in epidemiology[131]	http://www.strobe-statement.org/
PRISMA	Preferred reporting items for systematic reviews and meta-analyses[132]	http://www.prisma-statement.org/
SQUIRE	Standards for quality improvement reporting excellence[133]	http://squire-statement.org/
MOOSE	Meta-analysis of observational studies in epidemiology[134]	
COREQ	Consolidated criteria for reporting qualitative research[135]	
STARD	Standards for accurate reporting of diagnostic tests[136]	
TREND	Transparent reporting of evaluations with non-randomized designs[137]	http://www.cdc.gov/trendstatement/
SPIRIT	Defining standard protocol items for clinical trials[138]	https://www.spirit-statement.org/
CARE	Consensus-based clinical case reporting guideline development for CAse REports[53]	https://www.care-statement.org/
AGREE	A tool to improve reporting of clinical practice guidelines[139]	http://www.agreetrust.org/resource-centre/agree-reporting-checklist/
SRQR	Standards for reporting qualitative research: a synthesis of recommendations[140]	
CHEERS	Consolidated health economic evaluation reporting standards[141]	

[a]The main CONSORT Statement is based on the "standard" two-group parallel design. However, there are several different types of randomized trials, some of which have different designs (e.g. cluster, non-inferiority, and equivalence, or pragmatic trials), interventions (e.g. herbal medicinal, non-pharmacologic, or acupuncture), and data (e.g. harms), for which specific CONSORT Extensions exist. There are many extensions of PRISMA for different types of systematic reviews and meta-analyses.

Standardization of Pain-Related Outcome Measures

Regardless of the study design used, pain related research should assess and report valid, reproducible, and clinically meaningful outcomes to patients. Unfortunately, even though measures, such as joint range of motion, dynamometer measures of muscle strength, or radiologic evidence of successful spinal fusion, are often considered objective outcomes, they may not correlate well with pain, function, or health-related quality of life. On the other hand, pain, function, and health-related quality of life are more clinically relevant but are inherently subjective outcomes. Research suggests that pain can be measured in a reliable fashion, using measures such as numeric rating scale or visual analog scale. However, the meaning of these ratings has generated considerable debate.[142]

Importantly, although pain may reflect a patient's subjective experience, it is insufficient by itself, as self-reported pain scores often do not correlate well with the actual functional ability or status. Therefore pain related studies need to go beyond self-reports of pain and routinely examine outcomes that measure patients' behavior and function in their daily lives.

Since its inception in 2002, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has enlisted a broad array of experts in its efforts to improve the design, execution, and interpretation of clinical trials of treatments for pain.[143] IMMPACT recommends that trials routinely measure outcomes in multiple core domains, including pain, physical functioning, emotional functioning, global improvement, satisfaction with treatment, and adverse events, and includes a list of suggested measurement tools for each of these domains. In addition to addressing clinical trial outcomes, IMMPACT has developed a series of consensus reviews and recommendations regarding the conduct, interpretation, and reporting of trials for acute and chronic pain in adults, trials for acute pain in adults, and trials for pediatric acute and chronic pain.[144–153]

Assessing and Addressing Bias and Confounding in Clinical Research

Bias refers to any systematic process, effect, or error in the design or conduct of a study that favors one outcome over others.[154] Therefore studies at greater risk of bias are more likely to be misleading. Important types of bias include 1) *selection bias*, resulting in differences between groups other than the intervention of interest; 2) *performance bias* because of the effects of knowledge of patient assignment to different therapies; 3) *attrition bias* because of differences between those persons who do versus those who do not complete a study, and the level of participant compliance may remain a source of bias even among those who complete the study; 4) *detection bias* resulting in the differential interpretation of outcomes based on knowledge of assigned interventions; 5) *reporting bias* from the selective presentation results, typically those that are more favorable or statistically significant; and (6) *publication bias* from the preferential publication of studies reporting positive findings.

Methods to reduce the risk of bias in randomized trials include 1) use of adequate randomization and allocation concealment to prevent selection bias; 2) assessment of similarity of groups at baseline to detect important imbalances and failure of randomization to control for known confounders; 3) blinding of patients, caregivers, and research staff to avoid performance and detection bias; 4) low loss to follow up and use of intention-to-treat analysis to avoid attrition bias; 5) full reporting of pre-specified primary and secondary outcomes to avoid reporting bias and bias; and 6) for meta-analyses, efforts to locate unpublished studies and performance of graphical or statistical tests to determine whether publication bias and its potential magnitude may be present.

Given a randomized trial with a large enough sample and successful implementation of randomization, the problem of selection bias is eliminated mainly because all confounders, including those that are unmeasured or unknown, are equally distributed between groups, assuming successful randomization and a large enough sample size. Successful blinding of patients and research staff should largely eliminate performance and detection bias.[155]

As noted earlier, by their very nature, observational studies are susceptible to selection bias and confounding by indication, and they cannot blind patients and treating clinicians to the interventions received. Confounding refers to a situation in which the association between an intervention (I) and an outcome (O) is distorted by another factor (C).[156] This occurs when I is associated with C and when C is also an independent risk factor for O. For example, patients with back pain may have poorer outcomes when prescribed opioids compared to those not prescribed opioids if opioids are preferentially prescribed based on the presence of psychological comorbidities.[157] In fact, if back pain is also associated with psychological comorbidities, and if these are independently associated with poorer outcomes, a study that does not address this confounder will provide misleading results about the effects of opioid use on back pain. In addition, depressive symptoms and race were associated with increased healthcare utilization for chronic pain conditions.[157]

To address this during the assembly of the cohort, a study could match patients with key confounders such as psychological comorbidities or restrict enrollment to patients without psychological comorbidities. After a cohort is assembled, a study could evaluate baseline differences between groups in psychological comorbidities to assess the likely impact of this confounder and perform statistical adjustment through regression or other methods (e.g. propensity score matching) to control for its effects or stratification to evaluate how effects vary in defined subgroups.

Different types of evidence-focused studies differ in their susceptibility to bias. Therefore when evaluating the validity of a study, it is important to consider any design-specific methodologic shortcomings and their place in the study design hierarchy. For example, a well-conducted RCT will generally be less susceptible to bias than a well-conducted cohort study. When it comes to large-scale studies, key resources have become available with the emergence of big data science, access to large healthcare databases, modern epidemiologic methods, and large-scale computing power.[48] However, attention to the validity of data and analytic methods is still needed to determine the reliability of studies based on big data sources.

Statistical Concepts and Methods for Pain Outcome Studies

Basic Statistical Concepts and Terminology

Statistical methods are the cornerstone for analyzing and interpreting research data and form the basis for clinical decision making in pain medicine. Statistical methods can be divided into descriptive

and inferential methods. Descriptive statistics provide a concise summary of sample data,[158] whereas inferential statistics are used to draw conclusions about the larger population from which the data have been sampled.[159] For both the appropriate description of data and their analysis, it is important to consider the scale that has been applied to measure or collect the data and how the data are distributed. The following data types and measurement scales are distinguished[160]:

- Nominal data are characterized by discrete and mutually exclusive categories and are thus also referred to as categorical data. Such data have no natural or logical order. Examples include surgery type (e.g. with the categories general, orthopedic, cardiac, and other) and blood groups. A special case of nominal data is binary or dichotomous data in which there are only two categories, such as mortality (dead/alive).
- Ordinal data are similar to nominal data, but they do have a meaningful order and can be ranked. However, the distance between the ranks cannot be determined objectively, and it may not be the same across different ranks. A Likert-type scale to assess patient perception of a certain statement in terms of "strongly agree, agree, neutral, disagree, or strongly disagree" is a typical example. While there is a natural order, the distance between strongly agree and agree has no intrinsic meaning and may not necessarily be the same as that between "agree" and "neutral."
- Interval data are numeric, and equal distances or intervals have the same interpretable meaning. For example, the difference between 5° and 10° temperature on the Celsius scale is the same well-defined 5° difference as that between 20° and 25°. Interval scales such as the Celsius scale have an arbitrary rather than a natural zero point, precluding the calculation of ratios.
- Ratio data share the same characteristics as interval data and have an absolute zero point, which allows for the description of the data in terms of ratios. The difference in systolic blood pressure between 60 and 120 mm Hg is the same as that between 120 and 180 mm Hg, and a systolic blood pressure of 120 mm Hg can be said to be twice as high as 60 mm Hg.

Descriptive Statistics

The first step in converting raw data into useful information is to explore and describe the characteristics of the collected data. While it is theoretically possible, especially for small datasets, to show every single data point, this approach is usually tedious and may not provide a comprehensive overall impression of the data. Descriptive statistics are often used to reduce a large amount of data into a few characteristic numbers that provide a simple but informative overview of the typical values in the dataset and how the values vary.[161]

Nominal and ordinal data are typically summarized by the absolute frequencies (counts) combined with the relative frequencies (proportions or percentages) of observations within each category.

Interval and ratio data can also be shown as absolute or relative frequencies within specific bins or intervals of the range of values, as typically displayed with a histogram. Numerical data have two key characteristics that should typically be reported: the central tendency (the average value of the data) and the variability (the extent to which data spread around this average value). Data that approximately display a normal, bell-shaped distribution are appropriately described by their mean and standard deviation, whereas the median and quartiles are usually more informative for skewed data. Some ordinal data, such as numeric rating scale data, can also be meaningfully summarized by medians and quartiles.

Inferential Statistics

As studying an entire population of patients (e.g. all patients with complex regional pain syndrome type I) is usually not possible or feasible, clinical researchers commonly study a sample of patients to make inferences about the population of interest.[159] To draw meaningful conclusions, the sample should ideally be a random sample or must at least be representative of the population. However, samples are inherently affected by random sampling errors, and the estimates obtained from a sample generally differ from the underlying population parameters. For example, one would always expect to observe some between-group differences in the outcomes in a study comparing the effect of two treatments, even if the treatment effects are identical in the population. Moreover, when repeating the same study multiple times, using a different sample of the same population each time, one generally expects to observe different treatment effects in each study. It is thus inappropriate to base the conclusions of a research study on what has been observed in a particular study sample. Instead, statistical methods are needed (1) to determine whether the data provide sufficient evidence to claim an effect of the treatment or intervention in the population (or more generally, to claim a difference or association) and (2) to estimate what the "true" treatment effect (or any other estimate obtained from a sample) could plausibly be in the population from which the data were sampled.[159]

These two aims of inferential statistics are addressed by (1) hypothesis testing[162] and (2) effect size estimates and their confidence intervals.[159] Hypothesis tests and effect size measures with confidence intervals provide important and complementary information by showing two aspects of the same data set. Of note, the focus here is on the most commonly used approach to statistical inference, the so-called frequentist approach. Other approaches, such as Bayesian inference, are beyond the scope of this chapter.

Hypothesis Testing

An empirical scientific hypothesis can generally be proven false according to the principle of falsifiability. However, this cannot be proven true. An illustrative example is given by Karl Popper[163]: *"… no matter how many instances of white swans we may have observed, this does not justify the conclusion that all swans are white."* In contrast, the single observation of a black swan disproves the hypothesis that all swans are white.

In this context, a statistical hypothesis test does not test the actual research hypothesis that there is a treatment effect or difference between groups; instead, it tests the null hypothesis of no effect or no difference. In the standard superiority testing framework, the *p*-value obtained from a hypothesis test is the probability of observing an effect or difference as large as (or even larger than) the one that may be observed if the null hypothesis is actually true.[159]

Thus a small *p*-value raises doubt on the plausibility of the null hypothesis. If the *p*-value is below a pre-specified threshold (commonly 0.05), the null hypothesis is rejected in favor of the alternative hypothesis, and researchers conclude that there is an effect or difference.[162] However, note that a hypothesis test can only quantify the evidence against the null hypothesis but cannot actually disprove it. There is always a chance of reaching a wrong conclusion by either rejecting the null hypothesis when it is, in fact, true (type I error) or by not rejecting the null hypothesis when it is, in fact, false (type II error).[164]

Effect Sizes

Effect sizes quantify the magnitude of a relationship between variables, for example, between a variable that defines the treatment group and some outcome variable.[165] More than 70 different effect sizes have been described in the literature, including standardized or unstandardized mean differences, relative risks, odds ratios, or correlation coefficients. The effect size estimate should generally be accompanied by a confidence interval, which indicates the precision of the estimate and provides a range of values of what the effect (or any other estimate obtained in a sample) could plausibly be in the population from which the data were sampled.[166] Most commonly, a 95% confidence level is used, which indicates that approximately 95% of confidence intervals would be expected to contain the "true" population parameter on repeated sampling from the same population.

Effect sizes address the important question of whether the observed effect or relationship is clinically relevant instead of simply statistically significant.[159] Whenever the confidence interval contains a clinically important effect, a relevant effect cannot be ruled out even when it is not statistically significant. Conversely, a confidence interval that does not contain an important effect questions the clinical relevance, even when the result is statistically significant. Note that there is a close conceptual and mathematical relationship between confidence intervals and hypothesis testing. When a 95% confidence interval includes the null hypothesis value indicating no difference or no effect (e.g. 1 for a relative risk or 0 for a mean difference), the result is compatible with "no effect," and a corresponding hypothesis test would be nonsignificant at the 0.05 significance level.[159]

Standardized effect sizes allow the assessment of results across studies that report similar outcomes (e.g. pain relief) using different measures (e.g. 0–6 verbal rating scale, 0–10 numeric rating scale, and 0–100 visual analog scale). The standardized mean difference (also referred to as Cohen's d) is a unitless measure that standardizes results across studies by dividing the difference in the mean scores between groups by the pooled standard deviation. Each point in the effect size is equivalent to a difference of one standard deviation. Although the clinical interpretation of effect sizes can vary depending on the outcome being measured, the population assessed, and other factors, a general rule of thumb is that an effect size of 0.2–0.5 indicates a small effect; >0.5–0.8, a moderate effect; and >0.8, a large effect.[167]

Commonly Used Inferential Statistical Methods in Pain Research

This section describes some common hypothesis tests, methods to quantify relationships, techniques to assess agreement, and methods to pool data across studies. This section is by no means comprehensive, and a detailed description of how to use these methods in practice is beyond the scope of this chapter.

Importantly, each statistical method (test) has particular assumptions, for example, relating to the distribution of the data in the population from which the data were sampled. Statistical methods that are based on the assumption of a specific data distribution are referred to as parametric methods.[168] The assumed distribution is most often a normal distribution, but parametric methods are specifically designed for other distributions, some of which are also introduced below. Notably, the assumption of a specific distribution does not necessarily refer to the outcome variable itself, as often erroneously assumed by researchers, but, for example, to a normal distribution of the residuals (difference between observed and predicted values) in a linear regression model. In contrast to parametric methods, non-parametric methods do not assume a specific distribution.[168] However, both parametric and non-parametric methods also rely on other assumptions, for example, relating to the independence of observations. Assumptions are only somewhat covered here. Researchers should familiarize themselves with a particular method that they wish to use in more detail.

Statistical Methods for Continuous Outcomes

Continuous outcomes are often compared between two groups using two-sample t-tests,[169] and one-way analysis of variance (ANOVA) is used for more than two groups.[170] Test assumptions include normally distributed data and an equal variance in each group. Welch's t-test and Welch's ANOVA are alternatives when the assumption of equal variances is violated. The non-parametric equivalents, which can be used irrespective of the data distribution, are the Mann-Whitney *U* test (also known as the Wilcoxon rank-sum test or Wilcoxon-Mann-Whitney test) for two groups and the Kruskal-Wallis test for more than two groups.[171] For non-independent data (e.g. repetitive measurements in the same subjects at different time points), a paired t-test or repeated measures ANOVA, or their non-parametric counterparts, the Wilcoxon signed-rank test and the Friedman test, can be used.

When the analysis aims not to compare groups on a continuous outcome but to assess the strength of the relationship between two continuous variables, a correlation analysis is typically performed.[172] The correlation coefficient ranges from −1 to +1, with a value of 0 indicating no relationship and with absolute values increasingly closer to 1 indicating an increasingly stronger relationship. A positive coefficient indicates that the value of one variable tends to increase while the other increases, and a negative coefficient indicates an inverse relationship. Pearson's correlation coefficient is used to quantify a linear relationship between two normally distributed outcomes, whereas the non-parametric Spearman's rank correlation coefficient describes a monotonic relationship (i.e. one variable tends to consistently, but not necessarily linearly, increase or decrease while the other increases).[173]

Linear regression is used to test and quantify relationships between one or more independent variables (also termed predictor, covariate, or explanatory variables) and a continuous (dependent) outcome variable.[174] Two-sample t-tests and ANOVA are essentially special cases of linear regression with categorical independent variables. Linear regression with only one continuous independent variable provides a coefficient of determination that is identical to the squared Pearson's correlation coefficient.

However, linear regression is much more flexible than the techniques mentioned above and allows the simultaneous estimation of the relationship of several continuous or categorical variables with the outcome variable and determines whether the effect of one variable on the outcome depends on the value or level of another variable. It can be used to estimate how the outcome is expected to change for a particular change in each independent variable or predict the outcome value based on a set of predictor variables. Moreover, linear regression controls for the effects of other variables; for example, it can control for confounders in observational research or adjust for baseline imbalances in randomized controlled trials.[175] Extensions of linear regression, such as linear mixed effects models, are available for non-independent data.[176]

Statistical Methods for Count Data and Ordinal Data

Counts (e.g. hospital length of stay in days) are discrete rather than continuous, are often severely skewed, and may not satisfy the assumptions of linear models. Ordinal data are organized into discrete, ordered categories and can usually not be appropriately analyzed using methods that assume a normal distribution. Both count data and ordinal data can be compared between groups using the non-parametric tests listed in the above section, "Statistical Methods for Continuous Outcomes." However, flexible parametric regression-based approaches are also available to analyze count data (e.g. Poisson regression or negative binomial regression) and ordinal data (e.g. ordinal logistic regression).[174]

Statistical Methods for Categorical Outcomes

Pearson's chi-square tests can be used to test for an association between two nominal variables, for example, between treatment groups and a categorical outcome.[177] Fisher's exact test is an alternative to the Pearson's chi-square test when its assumptions regarding a minimum number of expected counts are violated. Pearson's chi-square tests and Fisher's exact tests rely on the assumption that the observations are independent of each other (e.g. no repeated measurements on the same subjects). McNemar's test can be used for paired data.[177]

Logistic regression was used to analyze relationships between one or more continuous or categorical independent variables and a binary outcome and estimate the probability that a binary outcome will occur, given the values of the independent variable(s).[174] As with linear regression and other regression models, logistic regression can be used to control for other variables (e.g. confounders). An extension of logistic regression and multinomial logistic regression is used for categorical outcomes with more than two levels.

Statistical Methods for Time-to-Event (Survival) Data

Researchers are often interested in analyzing the time until an event of interest occurs, which is typically an event such as the death of a patient. Therefore the term "survival analysis" is often used. However, any other well-defined event that has not occurred in all patients by the time the study ends can be analyzed as well.[178] The research interest is thus typically a combination of a binary outcome (has the event occurred?) and a continuous outcome (how long did it take until the event occurred?).

Another unique feature of time-to-event data and a key distinction from other continuous outcomes is that the actual survival time is unknown for patients who do not experience the event before the study ends or before they drop out of the study. Such patients are said to be censored, and all that is known is that the survival time is greater than the time until censoring. Statistical methods that can appropriately account for censored data are subsumed under the term time-to-event analysis or survival analysis and comprise a broad spectrum of techniques.[178]

A Kaplan-Meier curve is commonly used to plot the estimated probability of survival beyond a certain time point. Kaplan-Meier curves of different treatment groups plotted in one graph allow for a visual comparison, and the survival curves can be more formally compared with a log-rank test. Cox proportional hazards regression is particularly useful when the relationship between several independent variables and survival time is of interest or when the analysis needs to control for confounders. Results are commonly reported as hazard ratios, which are not the same as relative risks but can often be conveniently interpreted in a similar way.

Statistical Methods to Assess for Agreement

Agreement analyses are required to determine the degree to which multiple measurements of the same quantity produce the same result.[179] This can refer to measurements obtained by two different measurement techniques at the same time, measurements simultaneously performed by two different operators or raters using the same measurement instruments or rating scales, or measurements performed by the same person at two time points.

A Bland-Altman analysis is commonly performed to assess the agreement of two clinical measurement techniques that measure the same continuous outcome and determine whether the techniques can be used interchangeably. The Bland-Altman technique estimates the mean difference (representing the systematic bias) and how far apart the measurements are expected to be for the vast majority of measurement pairs (95% limits of agreement).[179]

The intraclass correlation coefficient (ICC) is frequently used to assess the inter- and intra-rater reliabilities of the measurement scales. There are several variants of the ICC, and the choice depends on factors, including whether the interest lies in absolute agreement or consistency and whether the same or different raters rate the subjects. For categorical data, Cohen's kappa quantifies the agreement between two observers beyond what would be expected by chance, and Fleiss kappa is used for more than two observers. For ordinal data, weighted Cohen's kappa is particularly useful as disagreements can be differentially weighted, depending on whether they refer to adjacent categories or distant categories (e.g. weighted kappa can account for the fact that there is less disagreement when one rater says "very poor" and the other "poor" than when one rates "very poor" and the other "excellent").[179]

Meta-Analysis

When researchers aim to summarize the current evidence on a particular research question, a systematic review methodology provides a rigorous approach to identifying relevant studies and extracting data in a structured and reproducible way.[180] Quantitative data of studies that are sufficiently similar in terms of patient population, treatments, and outcome measures are often pooled in a meta-analysis to obtain an overall summary estimate of the treatment effect (or any other effect) of interest. This summary effect is a weighted average of the effect size estimates from the individual studies, and weights are assigned based on how precisely a study estimates the effect size. As precision is primarily driven by sample size, larger studies generally receive more weight in a meta-analysis than do smaller studies.

Two main classes of meta-analyses were identified. A fixed-effect meta-analysis assumes that all variability in effect sizes between studies represents sampling error (i.e. that there is one common "true" effect size that all studies estimate).[181] The summary effect in a fixed-effect meta-analysis estimates this common effect size. In contrast, the random-effects meta-analysis allows for the true treatment effect to vary between studies. This is often a more realistic assumption, and thus it is usually recommended to perform a random effect meta-analysis because the setting,

patient population, disease characteristics, and how the treatment is administered tend to vary between studies. Under the random-effects assumption, the pooled effect size represents the mean of the distribution of true effect sizes.[181] The variation in true effect sizes between studies is referred to as statistical heterogeneity and provides important information on the extent to which a treatment effect would be expected to vary under different study conditions.

Important Statistical Considerations and Common Pitfalls

The Visual Analog Scale Controversy: Ordinal or Ratio Scale?

Pain intensity is commonly assessed using a visual analog scale (VAS). There is an ongoing debate about whether VAS scores should be considered ordinal or ratio data and whether parametric statistical methods can be appropriately used to analyze these data.[182–186] In fact, VAS scores have properties of both scales, and we advocate a pragmatic "it depends" approach.

First, several variants of the VAS score are used. A VAS score measured as a distance on a 100 mm line between the two extremes "no pain" and "worst imaginable pain" may essentially come quite close to a continuous measure with a natural zero point. However, some may question whether a score of 60 represents twice as much pain as 30. When the VAS score is rounded to or recorded as an integer between 0 and 10, similar to a discrete 11-point (0–10) Numeric Rating Scale (NRS) score, it loses some of its granularity and might be more like an ordinal scale. Second, not only the scale but also the distribution of data must be considered. VAS scores can be approximately normally distributed but also severely skewed, depending on whether they are concentrated around the center or around either extreme of the scale.[187] Third, the chosen statistical test may depend on the aim of the analysis. For simple between-group comparisons of VAS scores, irrespective of their measurement scale or distribution, there is little cost of using non-parametric tests.[187] On the other hand, corresponding parametric tests for between-group comparisons such as t-tests and ANOVA are quite robust against violations of the distributional assumptions, particularly for larger sample sizes,[169] and have been shown to generate valid results unless many patients report VAS scores at either extreme of the scale.[188] Moreover, parametric methods are more flexible and possible when more complex analyses are needed. When required, these techniques can be used when their assumptions are satisfied, and as stated earlier, these assumptions do not necessarily refer to the VAS score itself but to the residuals.

Of note, parametric models specifically designed for ordinal data, such as ordinal logistic regression, are also available[174] and can be useful for NRS-like data. A continuous ordinal regression modeling approach for ordinal data, with many ordered categories such as a 0–100-point VAS scale, has been suggested for VAS data that are extremely skewed.[187] Given the numerous possibilities, it is not very helpful (or prudent) to follow a dogmatic approach in which VAS scores must always be considered as either ordinal or interval data. It must always be analyzed using a specific parametric or non-parametric analysis technique. Instead, factors such as data distribution, the purpose of the analysis, and the sample size should also be considered when choosing a statistical method to analyze VAS data.

Sample Size Calculation

A key feature of any research study is an informed estimate of how many participants will be necessary to meet the study aims while avoiding an excessive number of patients. As outlined earlier in this chapter, two types of errors can occur when rejecting or not rejecting the null hypothesis based on a hypothesis test result, and the probability of making such errors decreases with increasing sample size. Thus the sample size should be chosen such that the probabilities of type I error (denoted as α) and type II error (denoted as β) are reasonably low.[164] The "power" of a study (also often referred to in the context of sample size calculations) is the probability of detecting a difference or effect when it is actually present in the population and corresponds to $1-\beta$.[162]

Common choices for the calculation of a sample size include an α of 0.05 and power of 0.8 (80%) or 0.9 (90%). The required sample size is also a function of the effect size that researchers want to be able to detect and the assumed variability of the data. While it is common to base the calculation on an expected difference or effect (e.g. based on pilot data or previously published literature), researchers are well advised to use the minimally important clinical difference (MICD) approach instead. Otherwise, the study may be underpowered to detect smaller yet clinically important effects.[164] Additional assumptions are required for more complex study designs, such as studies involving correlated data. When the aim of the study is not to test a specific hypothesis but rather to estimate some population parameters, the sample size should be chosen such that the parameter can be estimated with sufficient precision (with a confidence interval that is sufficiently narrow for the respective study aim).

Multiplicity Adjustments

When researchers test multiple hypotheses, each at a "standard" 0.05 significance level, the risk of a type I error markedly increases and can end up being much higher than the initially targeted α-level.[189] This situation commonly occurs when 1) several outcome variables are measured, 2) when the same outcome is repetitively studied at several time points, 3) when several groups are compared with each other in multiple pairwise comparisons, 4) when multiple subgroups are studied, or 5) when interim-analyses are performed.

When at least one significant test result from a set of tests would lead to a relatively strong inference, multiplicity adjustments are necessary.[189] For example, concluding that a particular treatment works because it is significantly superior to placebo in one out of four studied outcomes carries a considerable risk of being a false-positive result unless an appropriate adjustment is made. Similarly, comparing four treatment groups with each other and concluding that "treatment A" works better than "treatment D" because this difference happened to be significant can be severely misleading when the analysis was not adjusted for multiple comparisons. In contrast, no rigorous adjustment may be needed when the analyses are only exploratory or hypothesis-generating.[189]

The Bonferroni technique is probably the best known and definitely the simplest technique to adjust for multiple comparisons. With the Bonferroni technique, the significance criterion was set at α divided by the number of hypothesis tests (e.g. for $\alpha = 0.05$ and four tests, the significance threshold would be $0.05 \div 4 = 0.0125$), and only p-values smaller than the adjusted significance threshold were considered statistically significant.[189] Equivalently, the p-value can be adjusted by multiplying it by the total number of tests, and the adjusted p-value is then compared

against α. Notably, the Bonferroni adjustment was rather conservative. A variety of other adjustments are available and can often be automatically requested from the statistical software when performing tests involving multiple comparisons (e.g. for pairwise between-group comparisons after ANOVA).[190,191]

Distinguishing Between Statistical and Clinical Significance

As noted earlier in this chapter, inferences of a study generally refer to the population from which the data were sampled, not to the sample itself. In this context, it is incorrect to claim that something was "greater" or "better" (or something similar) based on observations in the sample in the absence of formal statistical analyses.

Even after statistical testing, results are often misinterpreted; for example, when clinically irrelevant between-group differences are highlighted as an important finding, the difference is statistically significant. It is important to realize that statistical significance and clinical importance are distinct concepts, and it is distinctly possible that irrelevant effects are statistically significant, whereas important effects may fail to reach the significance threshold.[159,192] Therefore the results of hypothesis tests should not be viewed in isolation but instead should be reported along with effect size measures and their confidence intervals. Ideally, researchers should define *a priori* what they consider a clinically important effect.

For example, with a large enough sample size, a study may report a difference in pain scores between the treatment and no treatment groups with an average of three points (95% CI: 0.7–5.3) on a 0–100 scale, with a *p*-value of 0.01. Although such a difference is statistically significant, the clinical significance and relevance of such differences are very small or negligible.

Another challenge in interpreting the results of studies that report means or differences in outcomes related to pain or function is that such data do not indicate whether they reflect a situation in which some patients experienced a very good outcome and others experienced no benefit or a situation in which patients generally experienced a small, similar average result.[193]

Studies commonly investigate a global approach for pain improvement by seeking a statistically significant decrease in the mean level of pain among their population. Among the most common outcomes measured is the effect on pain intensity and opioid consumption, outcomes that rely strongly on large sample sizes to achieve stronger and adequate statistical power. The clinical profile of a new intervention should include outcomes and parameters such as the delay and duration of the effect and the number of patients who report satisfactory pain control and tolerance of side effects.[194]

The MICD is defined as the smallest change in an outcome that a patient would perceive as clinically meaningful.[195] The IMMPACT group proposed defining the MICD as a 30% or greater improvement in self-reported pain and function.[196] The IMMPACT group also recommended that studies report the proportion of patients in each group who meet the MICD threshold. Based on the absolute difference between groups in the proportion of patients who experienced MICD, the number needed to treat to achieve one clinically meaningful outcome can be calculated [100 ÷ (the percentage of individuals with MICD in group A minus the percentage of individuals with the MICD in group B)].[197] Therefore in a study in which 40% of patients in group A experienced MICD for pain relief compared with 20% in group B, the number needed to treat is 100/20, or five. In contrast, in a study in which 40% of patients in group A experienced MICD compared with 37% in group B, the number needed to treat is 100/3, or 33.

Equivalence and Non-Inferiority Trials

In the conventional hypothesis testing framework (commonly termed superiority testing), a significant test result provides evidence against the null hypothesis. However, a non-significant test result means that there is insufficient evidence to reject the null hypothesis and thus does not provide evidence for the null hypothesis.[198] Therefore the interpretation that treatments are equally effective (or similar claims) when the difference is not statistically significant is flawed because there is no evidence for the null hypothesis.

Therefore superiority testing is not appropriate when the study aim is to demonstrate that a certain treatment (a new, alternative treatment) is as good as (equivalent to) or at least not worse than (non-inferior to) some other treatment (a standard treatment). An equivalence or non-inferiority study design and analysis are required instead.[199] As two treatments would likely never have identical effects (and if so, this would be impossible to prove), an equivalence study aims to show that the treatment effect differs by no more than a clinically acceptable margin. Similarly, a non-inferiority trial aims to show that one treatment is no worse than the other treatment by more than an acceptable amount. Because the results of equivalence and non-inferiority trials are sensitive to the definition of a clinically acceptable margin, it is considered essential that the equivalence or non-inferiority margin is defined *a priori* to avoid post hoc decision making.[199]

Multiple Related Outcomes and Joint Hypothesis Testing

Researchers often study the effects of a particular treatment on several related primary outcomes, such as pain scores and analgesic consumption in pain research. However, when the results are discordant, for example, if the treatment decreases pain but increases analgesic consumption, it can be challenging to reach a clear conclusion and invite *post hoc decision making*.[200] A further drawback of testing multiple primary outcomes in isolation is that a multiplicity adjustment is needed, as described above, which reduces the power of the analysis. Alternatively, researchers may declare one outcome as primary and the other as secondary and base their conclusions on the primary outcome. However, this approach can also be problematic when the outcomes are equally important.

It is often best to declare both (or more) related and equally important outcomes as primary outcomes and analyze them jointly in such situations.[200] An important feature of this joint hypothesis testing framework is that clear *a priori* decision rules are specified to decide whether an experimental intervention is superior to the comparison treatment or not. Commonly, the experimental treatment is only declared superior when it is superior to the comparison treatment for at least one of the outcomes and non-inferior for all other outcomes. Note that joint hypothesis testing does not require multiplicity adjustments, and at the same time, it ensures that a clear conclusion can be reached based on *a priori* decision rules.

Association Versus Causation—Confounding in Observational Research

A common mistake in observational research is to claim the effect of exposure on the outcome or to use other terminology suggesting a causal relationship. In contrast to a randomized trial, patients exposed to some factor of interest in an observational research usually systematically differ from patients who are not exposed.[175] For example, when studying a particular treatment observationally,

the treatment is not randomly assigned but may depend on several factors such as patient and disease characteristics. This leads to systematic differences between patients who have been versus those who have not been treated with the treatment of interest. Such differences, in turn, could themselves be related to the outcome and could thus explain some or perhaps even all of the observed differences in the outcome. It is thus inappropriate to conclude that the treatment leads to lower pain (or whatever the outcome may be); all that can be claimed is an association or relationship.

Factors that are causally related to the exposure and the outcome are referred to as confounders.[201] Statistical methods to control for confounding factors, such as multivariable regression or propensity score-based approaches, are available,[175,202] and they should be used when analyzing observational data. However, residual confounding, for example those caused by unobserved factors, is nevertheless possible; thus causal inferences based on observational data should generally be avoided.

Concluding Statements

EBM offers a formal set of steps for clinicians to effectively interpret the results of a clinical research ("how to read a paper") and apply them in their practice. The GRADE system is widely used to grade the quality of published evidence and the strength of recommendations. This chapter has discussed different types of clinical studies that focus on pain outcomes and have different levels of evidence (from case reports and case series to complex randomized controlled trials, systematic reviews, and meta-analyses). Furthermore, we discussed key statistical methods used when planning these studies or analyzing the data.

Key Points

- A case report shares with the medical community, novel, rare, or atypical features identified in a patient.
- A cross-sectional study determines the prevalence of a disease at a given point or period in time.
- A case-control study determines the relationship between the absence or presence of a single outcome (disease) and one or more previous possible contributing factors (exposures).
- A nested case-control study is a case-control study in which cases and controls are selected from members of an existing longitudinal cohort.
- A cohort study determines the relationship between a single contributing factor (exposure) and one or more possible outcomes (diseases).
- A randomized controlled trial is a type of controlled clinical trial predicated on participants being assigned to possible exposures or interventions purely by play of chance.
- A CRT is a trial in which individuals are randomized into groups; the group as a whole is randomized, and not the individual.
- A meta-analysis combines and compares the results of multiple scientific studies that are sufficiently similar to obtain an overall summary estimate of the effect of interest. This summary effect is the weighted average of the effect size estimates from the individual studies.
- Healthcare economic evaluation techniques promote efforts to provide optimal care while controlling unnecessary or wasteful healthcare expenditures to focus on delivering high value, cost-conscious healthcare.
- Bias refers to any systematic process, effect, or error in the design or conduct of a study that favors one outcome over others, whereas confounding refers to a situation in which the association between an intervention and an outcome is distorted by another factor.
- The *p*-value obtained from a hypothesis test is the probability of observing an effect or difference as large as (or larger than) the one that may be observed if the null hypothesis (that there is no effect or no difference) is true.
- Effect sizes quantify the magnitude of a relationship between variables, for example, between a variable that defines the treatment group and some outcome variables.
- Statistical methods have been developed to analyze data, including continuous outcomes, count data, ordinal data, categorical outcomes, time-to-event (survival) data, agreement, and diagnostic accuracy.
- Sample size calculation provides an informed estimate of how many subjects will be necessary to meet the study aims while avoiding an excessive number of patients. It is a key feature of studies to minimize the probability of type I and II errors.
- Testing multiple hypotheses increases the probability of type I errors. This may be avoided by joint hypothesis testing when the outcomes are equally important. Another solution is multiplicity adjustment, such as the Bonferroni technique, which consists of dividing the significance criterion by the number of hypothesis tests.
- When interpreting clinical research results, a key concept is that statistically significant results are not always clinically meaningful. Calculation of the MICD, effect size, and confidence intervals may help distinguish between the two.
- A non-significant test result does not allow the conclusion that the two treatments work equally well. Instead, an equivalence study can show that the treatment effect differs by no more than a clinically acceptable margin. A non-inferiority trial shows that one treatment is no worse than the other treatment by more than an acceptable amount.
- Statistical methods are available to control for confounding factors, such as multivariable regression and propensity score-based approaches.

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84

Outcome Domains and Measures in Acute and Chronic Pain Clinical Trials

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An important feature in the planning of any clinical trial regards the decisions made as to the outcome criteria that will be used to evaluate treatment efficacy. Traditionally, the outcomes used in both acute and chronic pain research have been a reduction in pain intensity and presence of adverse effects (AEs). However, more recently, other important factors have been identified that should be included as outcome measures.

Several groups have reviewed and suggested outcomes to be considered in clinical trials, both general and well as disease specific (e.g. the Initiative on Methods, Measures, and Pain Assessment in Clinical Trials; IMMPACT),[1–3] Core Outcome Measures in Effectiveness Trials (COMET),[4] outcomes measures in rheumatology,[5–7] NIH task force,[8] and Veterans Health Administration Workgroup.[9] The objective of COMET is the development and application of agreed standardized sets of outcomes, known as "Core Outcome Sets" (COS). They noted that the sets represent the minimum that should be measured and reported in all clinical trials of a specific condition and that COS are also suitable for use in routine care, clinical audit, and research, other than randomized trials. They stated that the existence or use of a COS does not imply that outcomes in a particular study should be restricted to those in the relevant core outcome set. COMET "aims to collate and stimulate relevant resources, both applied and methodological, to facilitate the exchange of ideas and information, and to foster methodological research in this area."[4] A representative example of the group's publications to accomplish this primary aim is a COS on effectiveness trials.[10]

This chapter will discuss the outcome domains and measures advocated by several groups, namely, IMMPACT,[1,2] pedIMMPACT,[3] and APS-POQ-R[11] as they provide comprehensive recommendations. The domains enumerated by IMMPACT, pediatric IMMPACT (pedIMMPACT), and American Pain Society-Post-operative Questionnaire-Revised (APS-POQ-R), (i.e. pain; physical functioning; emotional functioning; participant ratings of improvement and satisfaction with treatment, symptoms and adverse events; and participant disposition [adherence to the treatment regimen and reasons for premature withdrawal from the trial]) were developed by a set of individuals with experience in conducting clinical research, quality improvement, providing clinical care, and several lay advocates. It is important to acknowledge that patients may have different ideas regarding the most important outcomes for them. For example, when adults with chronic pain were surveyed, they affirmed that the set of domains recommended by these groups were important to them. However, they also described the importance of improving sleep quality, reducing fatigue, and improving the enjoyment of life following treatments.[12] We will review domains and measures for acute and chronic pain for adult and pediatric populations specifically proposed by IMMPACT, pedIMMPACT, and APS-POQ-R. Moreover, patient satisfaction, a reflection of the interaction of the different domains, will be discussed in detail as a complement to the others proposed.

Besides considering important outcome domains, we will discuss general issues in selecting appropriate outcome measures to address the research questions of interest and to describe some of the most frequently used instruments in clinical trials conducted in anesthesiology and pain medicine. We do not intend to present an exhaustive list or provide a comprehensive critique of the psychometric properties and the strengths and weaknesses of all measurement tools enumerated. Instead, we will discuss several measures that have been selected by knowledgeable investigators of clinical trials in anesthesiology and pain medicine. We have included an extensive set of references to accompany this chapter and that are electronically available that readers can consult depending on their particular interests. Note, that although we focused on measures that can be considered for use in clinical trials, many of the measures described should be considered appropriate for use in clinical practice.

Selecting Outcome Measures for Use in Clinical Trials

Although the outcome domains for acute and chronic pain trials in both adults and children overlap, the measures selected will vary to some extent based on the age of the patients and their ability to comprehend the concepts entailed in the measures, the amount of patient burden required to respond, and the experimental context (e.g. developmental stage; cognitive limitations, postoperative vs. chronic pain state). There are instances where the same measures can be used across different ages, type of pain, and treatment contexts (e.g. perioperative vs. chronic). For example, a single question regarding pain severity or several questions regarding mood, ability to engage in functional activities, and the presence of AEs may be acceptable in both acute and chronic pain trials.[11] Similarly, simple ratings of pain intensity may be used across certain ages (eight to 18) but not for all (e.g. neonates) or those with the inability to communicate (unconscious or otherwise cognitively

TABLE 84.1 Factors to Consider in Selecting Pain Reported Outcome Measures

- The clarity of the instructions and items contained in a scale (Can the population for whom it is intended understand the instructions and the meaning of the individual items?)
- Respondent demands (i.e. Does the measure have acceptable *patient burden*?)
- The *validity* of the measure (Does an instrument measure what it is designed to measure?)
- The *reliability* of the measure (Does the instrument demonstrate that it consistently measures the construct intended?)
- The items contained in the instrument all measure the construct of interest and the context of use, and the items in the scale demonstrate reasonably high correlations with each other - sometimes referred to as *internalconsistency*, Cronbach's alpha, or *coefficient alpha*
- Will the same results occur if the instrument is completed at two points in time without any intervention - sometimes referred to as *test-retest reliability or consistency* over time?
- The measure is *responsive* to change (Are treatments capable of demonstrating change on this measure?)
- Are there appropriate *normative data* to which the current sample is to be compared available?
- Does the measure place excessive demands/burden on the person responsible for scoring it (Are there lengthy and complex scoring algorithms required?)?

compromised patients). The availability of appropriate normative data for the sample to be included in a trial becomes an essential consideration in selecting from available measures.

Throughout this chapter, we will describe a wide range of measures, particularly patient reported outcome measures (PROMs). These measures are essential in assessing a subjective state such as pain and the impact that pain has on all domains of an individual's life—physical functioning, emotional, and broadly conceptualized as health-related quality of life (HR-QoL) as emphasized by IMMPACT, pedIMMPACT, and APS-POQ-R. In selecting from the vast array of general, disease specific, and treatment specific PROMs available, investigators, as well as clinicians, need to pay attention to a host of factors outlined in Table 84.1. The set of concepts outlined are typically referred to as the psychometric or clinometric characteristics of the measure or procedure.[13]

For measures dependent on physical assessment (1) the *inter-rater reliability* (Would the same result be obtained from two or more raters of the same patient?) and (2) *intra-rater reliability* (Would the same rater obtain comparable results if the procedure is performed on the same patient at two points in time?) need to be considered. For physical assessment, it is important to acknowledge the importance of training for examiners to maximize agreement.[14]

Clinical Significance vs. Statistical Significance

Once an outcome measure is selected, it is important to consider the amount of change that would have to occur following treatment for the results to be meaningful. Traditionally, the emphasis has been on statistically significant differences. For example, a 30% reduction in pain on an 11-point numeric rating scale (NRS) has been accepted as demonstrating a statistically significant result.[15] However, a statistically significant outcome can be affected by the sample size included in the study. A small but statistically significant result in a study with a very large sample may have little clinical importance and, therefore, may be trivial.[16] More recently, attention has been given to the concept of clinical meaningfulness as an important complement to statistical significance. Several studies have been conducted to identify the amount of change on any scale that would be required for the change to be clinically significant (i.e. meaningful, important to patients and providers).[17] There are several ways to determine clinical significance, with an anchor-based approach being most appropriate. Many anchor-based approaches for establishing criteria for identifying important change rely on a global item completed by the patient as the anchor for within person changes indicating that the change is meaningful. For example, to determine whether there were important changes in pain over the course of treatment, patients' pain could be assessed at baseline and again at the end of the trial, at which point they would also be asked if they were "better," "about the same," or "worse," compared with the beginning of the trial. These improvement ratings would then serve as the standard with which to evaluate the importance to the patient of whatever changes in pain had occurred during the course of the trial.

Whenever an anchor-based approach has been conducted to identify a meaningful clinically important difference (MCID) has been established in should be used[18] to determine whether the results obtained are clinically important. However, when an MCID has not been formally determined, a reasonable rule of thumb is to use distribution-based criteria, either the effect size or change, based on the standard error of measurement (SEM). An effect size of 0.50 (i.e. one-half the standard deviation) may be a practical criterion to use when beginning to investigate important changes in PROM.[19,20] SEM provides a measure of within person change that is less dependent on a specific sample because it incorporates both the standard deviation and the reliability as a proxy for the MCID.[18] In several studies, 1 SEM approximated the MCID threshold.[21]

Outcome Domains and Measures in Adult Acute Pain Trials

For acute pain trials, both IMMPACT[22] and APS-POQ-R[11] recommend that intensity and pain relief should be the primary outcome domains for and clinical trials and quality improvement (QI). IMMPACT suggested that an NRS be used. Verbal rating scales (VRS) for pain intensity ("no pain," "mild pain," "moderate pain," "severe pain") and amount of pain relief ("no relief," "little relief," "some relief," "moderate relief," "complete relief") have also been frequently used. APS-POQ-R recommended using an 11-point NRS (zero, no pain, to ten, worst pain imaginable) for two questions—pain at its *least* and at its *worst* over the past 24 h (note that the interval could be shorter depending on the patient's ability to respond and the research question, for example, 6 h). In addition, APS-POQ-R recommended a third question, the percentage of time the patient experienced severe pain in the past 24 h. An additional outcome of potential interest noted was time to first analgesic intake. Consideration should also be given to the timing of pain assessment during recovery. Pain ratings should also pain at rest (e.g. lying down) and when appropriate on specific movements (e.g. coughing, repositioning, ambulating).

The occurrence of AEs is an important outcome domain. The usual side effects should be observed and when patients are able directly reported by them. APS-POQ-R specifically suggests assessing the severity of four common postoperative side effects, nausea, drowsiness, itching, and dizziness, with each rated on an 11-point NRS when patients are capable of making such ratings. A caution regarding solicitation reports of side effects from patients is noteworthy. Asking about the presence of specific side effects may

prompt patients to report the occurrence of these and increase the number, whereas an open-end question asking patients if they have experienced or are experiencing "any" side effects may lead to missing some that the patients do not consider reporting. Thus there are some trade-offs with either approach.

The impact of pain and treatments on other AEs have also been assessed. For example, studies have focused on the degree of the patient's sedation (e.g. observer's assessment of alertness/sedation scale,[23] Ramsey sedation scale),[24] sleep quality or interference (Pittsburgh Sleep Quality Index,[25] Epworth Sleepiness Scale),[26] or the presence of delirium.[27] The Mini-Mental Status Examination (MINI) has been used to measure sedation as well as the cognitive ability of the patient.[28] The Opioid-Related Symptoms Distress Scale has been employed to look specifically at symptoms related to opioid intake; these include difficulty passing urine, headache, feeling of lightheadedness, fatigue, or weakness.[29] It should be noted that there is no single assessment tool designed to assess all the side effects, mostly the focus is on a specific one.

Both IMMPACT and APS-POQ-R suggest that physical functioning is an important outcome domain for acute pain clinical trials. APS-POQ-R suggests asking four questions related to the inference of pain with physical functioning, specifically, sedentary activities (i.e. turning, sitting up, repositioning), activities out of bed (i.e. walking, sitting in a chair, standing at the sink), and falling asleep and staying asleep. They suggest that each of these questions should be rated on an 11-point NRS. For perioperative studies, it was suggested that time to first bowel movement, length of intensive care unit (ICU) and/or hospital stay, and patient satisfaction be considered as appropriate. For longer duration acute pain studies as in the recovery room, intensive care, or emergency department, IMMPACT and APS-POQ-R recommended additional outcomes domains for physical function such as the timing of ambulation. Assessment of other functional activities to consider will depend on the context and duration of pain. Some of the measures used for assessing physical functioning in chronic pain discussed below may be appropriate to consider depending on the time interval.

Emotional functioning is the least studied outcome domain in postoperative pain studies, although it is important as it may influence the rate of recovery, length of hospital stay, and patient satisfaction with the treatment. APS-POQ-R recommends four questions rating emotional functioning, each on an 11-point NRS scale, namely how anxious, depressed, frightened, and hopeless patients felt. In the immediate postoperative period, these simple measures of emotional distress may be most reasonable to decrease patient burden. However, in longer duration acute pain trials (e.g. days, weeks), more comprehensive tools for assessing anxiety may be considered, such as the Yale Preoperative Anxiety Scale,[30] the Hospital Anxiety and Depression Scale (HADS),[31] and the Generalized Anxiety Disorder-7 (GAD-7).[32] There are multidimensional tools used in chronic pain investigations (discussed below) that have been utilized in acute pain studies, when reasonable given the context of acute pain (e.g. emergency department, ambulatory care clinic), that assess several outcome domains (Table 84.2). These include the Brief Pain Inventory (BPI), Medical Outcomes Study Short Form Health Survey SF-36 and its modifications (SF-12 and SF-8), and EuroQoL 5-D.[33–39] These instruments have been shown to have very good psychometric properties when used with chronic pain samples. However, they should be cautiously used as they were not specifically designed or validated for use in the immediate postoperative period.

Another multi-domain measurement tool is the International Pain Outcomes Questionnaire (IPO),[40] developed by the European Commission-funded PAIN OUT project. IPO includes domains of pain intensity, physical and emotional, functional interference, side effects, and perceptions of care. The questionnaire was finalized after two modifications: (1) phase one to five questions were added to the 14 item APS-QoR-R, (2) phase two to eight questions were removed from the questionnaire. As a result, the final version had high internal consistency reliability. However, although promising, to date, not many publications have reported results using the IPO.

TABLE 84.2 Outcome Domains Covered by Postoperative Pain Measures

Measure	Pain	Physical Functioning	Emotional Functioning	Side Effects	Patient Satisfaction
BPI	+	+	+		
MPQ	+		+		
SF-36	+	+	+		
SF-12	+	+	+		
SF-8	+	+	+		
EuroQoL 5-D	+	+	+		
QoR-40	+	+	+	+	
QoR-15	+	+	+	+	
APS-POQ-R	+	+	+	+	+
IPO	+	+	+	+	+

APS-POQ-R, American Pain Society Patient Outcome Questionnaire Revised; *BPI*, Brief Pain Inventory; *EuroQoL 5-D*, European Quality of Life 5-Dimensions; *IPO*, International Pain Outcomes Questionnaire; *MPQ*, McGill Pain Questionnaire; *QoR*, Quality of Recovery (QoR-40 and QoR15 for the 40 item and 15 item questionnaire, respectively); *SF-36*, Medical Outcomes Study Short Form-36 (SF-12 for 12 items; SF-8 for eight items).

From: Benzon HT, Mascha E, Wu C. Studies on postoperative analgesic efficacy: focusing the statistical methods and broadening outcome measures and measurement tools. *Anesth Analg.* 2017;125:726-8.

Perhaps the comprehensive measure and one that has received the greatest amount of research is the set of quality of recovery (QoR) instruments.[41–43] These were initially developed and validated for use in the perioperative period. The QoR is the most commonly used instrument in postoperative pain studies, and it appears that a shortened version, the QoR (QoR 9, QoR 15), may be a reasonable alternative, and thus we describe it in some detail.

Myles group formulated a comprehensive QoR40, simpler nine item QoR questionnaire, and more recently, a QoR15.[41–43] The set of QoR tools measure five dimensions of health: pain, physical comfort, emotional state, psychological support, and physical independence. All of the QoR instruments have very good validity and reliability and excellent completion and return rates. The MCID, i.e. minimal change in score that indicates a meaningful change in a patient status —improvement or deterioration—was noted to be 0.92, 6.3, and 8.0 for the QoR, QoR40, and QoR15, respectively.[44]

The QoR 15, which has fewer items than the QoR 40 and with similar psychometric properties, has fewer items and takes 3 min to complete (Figure 84.1). Utilization of the QoR15 (or the QoR40), the IPO, or the APS-POQ-R includes most of the outcome domains recommended by the IMMPACT group.

QoR-15 Patient Survey

Date: _ _ /_ _ / _ _ Study #: __ __ ___ ___

Preoperative ☐ Postoperative ☐

PART A

How have you benn feeling in the last 24 hours?

(0 to 10. where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2.	Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3.	Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4.	Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6.	Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7.	Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8.	Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9.	feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10.	Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0. where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12.	Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13.	Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14.	Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15.	Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time

• **Figure 84.1** Q0R 15 Patient Survey.

While patient satisfaction is not directly addressed in the QoR instrument (Table 84.2), the authors noted that quality of recovery is directly related to patient satisfaction.[45] In one study, the investigators noted a strong association between the original nine item QoR and patient satisfaction. Since the QoR does not specifically assess patient satisfaction, investigators should consider including a measure of patient satisfaction when using the QoR.

Outcome Domains for Adult Chronic Pain Clinical Trials

As noted, based on a review of the literature, IMMPACT recommended that six core domains should be considered in *chronic pain* clinical trials: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; and (6) participant disposition (adherence to the treatment regimen and reasons for premature withdrawal from the trial) (Table 84.3).[2] Moreover, IMMPACT indicated that other domains might be considered depending on specific research questions addressed in the trial (e.g. clinician or surrogate ratings of improvement, interpersonal functioning). The group emphasized that there are exceptions to using all the domains but the rationale for not including a domain should be explained. Additionally, the group acknowledged that statistically significant effects for all the domains were important to establish the efficacy of the intervention, however, investigators should indicate the primary outcome(s) of interest.

The IMMPACT domains depend primarily on patient self-report (PROMs). Self-reports assess experience and behavior at a single point in time or evaluate an experience averaged over a recalled period (e.g. last seven days).[46] However, pain can fluctuate over time depending on the activity and mood of the patient and on environmental factors that can impact emotional or physical function. Thus more frequent ratings using daily diaries and real-time data acquired electronically may be useful ways to evaluate the impact of treatments as related to circumstances that are influenced by a variety of factors (e.g. pain intensity at rest versus during movement, time of day as symptoms may vary).

TABLE 84.3 Core Outcome Domains and Measures for Chronic Pain Clinical Trials

Outcome Domain	Outcome Measurement Measures
Pain	11 point (zero to ten) numeric rating scale of pain intensity Usage of rescue analgesics Categorical rating of pain intensity (none, mild, moderate, severe)[a]
Physical functioning[b]	Multidimensional Pain Inventory interference items Brief Pain Inventory interference items
Emotional functioning[b]	Beck Depression Inventory Profile of Mood States
Participant ratings of global improvement and satisfaction with treatment	Patient Global Impression of Change
Symptoms and adverse events	Spontaneously reported adverse events and symptoms and use of open-ended prompts
Participant disposition	Information on patient recruitment, and progress through the trial (CONSORT diagram)

[a]Recommended when numeric ratings not feasible.
[b]Use one of the two recommended tools.

From Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2003;106:337–45.

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113:9–19.

Pain

The assessment of pain often involves determining the extent of the patient's disease or injury and whether the patient's behavior is "appropriate" or "reasonable" for the disease or injury.[47] These questions are evaluated by taking the patient's history and physical examination, both of which require interpretation by a clinician and his or her experience and through assessment measures. NRS, VRS, and visual analog scales (VAS) are reliable, and all consistently show greater ability to detect improvement after treatment. However, IMMPACT recommended the 11-point NRS because of concerns raised about the ability of older populations to understand the use of VASs, and they can be difficult to use during telephone interviews and on electronic devices such as smart telephones. The VRSs tend to be limited by the number of categories (e.g. three, five, seven) used and thereby restrict the range of the scale. Therefore the ability to detect small but potentially meaningful change maybe limited.

A caution about self-reporting pain intensity. Although it seems deceptively simple to ask patients how much they hurt, several factors can influence the rating. For example, how much they hurt now, on average (usual), or when pain is at its worst? Over what period, last hour, days, week? Compared to what—"worst pain imaginable," "worst pain ever had," "pain before starting treatment," "during the last surgery I had"? Thus although a patient will readily respond to the question, patients may interpret the question differently, and the wording of the question can influence the responses obtained. Nevertheless, the gold standard for pain assessment depends on the patient who responds to the questions at the current time.

In addition to assessing the intensity of pain, measures such as the short form of the McGill Pain Questionnaire-2-Revised,[34,48] have been developed to assess descriptors characterizing pain (e.g. dull, aching, stabbing). These descriptors may differentiate nociceptive pain from neuropathic pain, and treatments may affect some of the characteristics but not others. Several measures have been developed to assess characteristics specifically associated with neuropathic pain, and these are described below.

Neuropathic Pain Measures

There are two sets of neuropathic pain measures, those that determine the qualities and progress of the neuropathic pain syndrome and questionnaires that determine whether a pain syndrome consists mostly of neuropathic features.[49] The former tools include the Neuropathic Pain Scale (NPS) and Neuropathic Pain Symptom Inventory (NPSI).[50–52] These measures assess the distinct pain qualities associated with neuropathic pain, determine the efficacy of different treatments, and help elucidate the mechanism(s) of

the effect of such treatments. However, the NPS and NPSI do not differentiate patients with neuropathic pain from patients with non-neuropathic pain

Four questionnaires determine whether a pain syndrome are mostly neuropathic or not: the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS),[53] the Neuropathic Pain Questionnaire (NPQ),[54,55] the neuropathic pain diagnostic questionnaire, Douleur Neuropathique called the DN4,[56] a Neuropathic Pain Screening Questionnaire (NPSQ) designed for use in a primary care setting,[57,58] and the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2).[59] The LANSS is a seven item pain scale that consists of a grouped sensory description and sensory examination with a simple scoring system. The first five questions ask for the presence of unpleasant skin sensation, appearance of the skin, increased sensitivity of the skin to touch, sudden bursts of electric shock-like sensations, and hot or burning skin sensations. The last two questions involve sensory testing for the presence of allodynia and altered pinprick threshold. A different number of points, relative to their significance to neuropathic pain, are given positive answers for a maximum of 24 points. A score of <12 makes it unlikely that the patient's symptoms are neuropathic in nature, whereas a score >12 makes neuropathic mechanisms likely to be contributing to the patient's pain. The NPQ contains 12 items to help differentiate neuropathic pain patients from non-neuropathic pain patients. A stepwise discriminant analysis of the 12 NPQ items identified three items as significant predictors. These included tingling pain, numbness, and increased pain because of touch. From these three items, the authors offered a short form of the NPQ.[55] The French neuropathic pain group developed the DN4. Although there are four main questions, the DN4 is a ten item questionnaire of sensory descriptors and signs related to bedside sensory examination. A cutoff score of four predicts a neuropathic pain syndrome. The NPSQ has six questions, "higher scores suggested a neuropathic component."[58] The LANSS and DN4 have similar predictive values, sensitivities, and specificities. The short form NPQ and the NPSQ have lower values.

The SF-MPQ-2[59,60] includes descriptors commonly reported by patients with neuropathic pain and descriptors that are most commonly reported by patients with various nociceptive pain conditions (e.g. osteoarthritis). The SF-MPQ-2 consists of 21 descriptors, each rated on an 11 point NRS from "no pain" to "worst possible pain." Based on a factor analysis, the SF-MPQ-2 comprises four factors, namely, four readily interpretable subscales—continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors. The reliability, validity, and subscale structure of the revised SF-MPQ-2 were examined in responses from individuals with diverse chronic pain syndromes and in a sample of patients with painful diabetic peripheral neuropathy who participated in a randomized clinical trial. This measure has been shown to reliably and validly distinguish between these two groups of patients and has been reported to be reliable when assessing patients with chronic pain. It has also shown to be both reliable and valid when assessing acute back pain patients.[59]

Physical Functioning

Physical functioning can be assessed in three primary ways: validated performance-based outcome measures of pain-related physical functioning (e.g. 6-min walk test [6MWT], timed sit-to-stand test),[61,62] patient self-report (PROMs), and recording of activity taking place in real-time (e.g. ambulatory measures of activity such as using accelerometry).[63] Each of these approaches has strengths and limitations, and as a set, they may provide complementary information, but they are not interchangeable. For example, clinical assessment of physical functioning provides an objective indication of functional capacity but may not reflect patients' perspectives on the impact of pain on their functional activities in their daily lives. In addition, electronic measures of performance acquired during routine daily activities may vary from what is observed in a constrained clinical setting where patients know they are being observed and have different levels of motivation. Thus as noted, they provide complementary information, and the one(s) selected will depend to some extent on the research question.

IMMPACT, in conjunction with outcomes measures in rheumatology (OMERACT), published an extensive list of PROM of physical functioning clinical, observer, and laboratory measures of physical functioning, and naturalistic assessment in the patient's lived environment.[64] Selected measures are listed in Table 84.4. These include tools for pain-related and general physical functioning/activity measures,[33,65–68] activities of daily living,[35,69–71] disease,[72–76] and site-specific physical functioning.[77–84] Additionally, IMMPACT-OMERACT enumerated several clinical, observer, and laboratory tools available and grouped them by sub-domain, including mobility or activity measures,[85–87] general physical functioning,[62, 88–92] multi-activity tests,[93,94] and site-specific domains[95–98] (Table 84.4). The set of measures and procedures that we included in our table is illustrative but not exhaustive. IMMPACT/OMERACT recommended the timed up and go (TUG),[85] the 6MWT,[61,86] and the Short Physical Performance Battery (SPPB)[93] for performance measures of physical conditioning. Interestingly, the 6MWT has been used in studies in regional anesthesia and acute pain.[99] The reliability of electronic recording (e.g. accelerometry, actigraphy) has been established.[63,87,100]

Employment status has been used to reflect physical conditioning, usually in the form of a binary question. Other questions include sick leave, short-term disability, and absenteeism from work. While there are validated measures that assess the patient's work activities,[101–104] these tools are not commonly used at the present time but may be used depending on the research question being addressed.

For interference with function and, as noted previously, psychometrically validated HR-QoL include the SF-36 and variants[35] while the Pain Disability Index (PDI)[66,105] is a general measure of physical functioning**.** Other comprehensive measures that evaluate physical functioning include the West Haven-Yale Multidimensional Pain Inventory (MPI),[67] and SW Sickness Impact Profile (SIP),[69,106,107] the EuroQoL, and the Nottingham health profile.[108,109] Several disease specific measures have been developed. Some examples of disease specific measures include the WOMAC for osteoarthritis,[75,110] and Roland Morris back pain Disability Questionnaire (RMDQ) for back pain,[72,73] the Neck Disability Index (NDI);[80,111] and the Fibromyalgia Impact Questionnaire Revised (FIQ-R)[74,112,113] (see Table 84.4).

Emotional Functioning

Psychological variables are involved in the initiation, maintenance, and prolongation of chronic pain.[114] These variables include beliefs, appraisals,[115,116] and thought processes, catastrophizing (assuming the worst possible outcome),[117] sense of control/helplessness,[118,119] self-efficacy,[120,121] coping,[122,123] moods and behaviors,[124] depression,[125,126] and fear, and anxiety.[116,127] These psychological determinants are extensively discussed in Chapters 14 and 22.

There are two ways to assess emotional functioning. When a specific psychiatric diagnosis is required, interview-based methods

TABLE 84.4 Selected Measures on Physical Functioning for Use in Chronic Pain Studies

Patient Reported Measures	Measurement Tools
Pain-related physical functioning/activity	Pain Disability Questionnaire (PDQ)
	Pain Disability Index (PDI)
	Multidimensional Pain Inventory (MPI)
	Brief Pain Inventory (BPI)
General physical functioning/activity	MOS 36 Item Short Form Health Survey (SF-36)
	Sickness Impact Profile (SIP)
	PROMIS Physical Functioning Item Bank
Activities of Daily Living	Center for Disease Control and Preventions' Healthy Days Measures (CDC HR-QoL-14)
	Duke-UNC Health Profile
	Katz Index of Independence in Activities of Daily Living
Disease Specific physical activity/ functioning	Roland Morris Disability Questionnaire (RMDQ)
	Fibromyalgia Impact Questionnaire Revised (FIQ-R)
	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
	McMaster Toronto Arthritis (MACTAR) Patient Preference Disability Questionnaire
	Musculoskeletal Functional Limitation Index
Site-specific physical functioning/activity	Disability of the Arm, Shoulder and Head (DASH)
	QuickDASH
	Oswestry Disability Index (ODI)
	Neck Disability Index (NDI)
	Western Ontario Rotator Cuff Index
	Patient-rated Tennis Elbow Evaluation
	Boston Carpal Tunnel Questionnaire
	Foot and ankle ability measure
Clinical, observer, and laboratory tools	
Mobility or Activity measures	Timed Up and Go (TUG)
	6-minute-walk test
	Actigraphy (Not a measure but an electronic device worn by an individual that records activity levels)
General physical functioning	Stair climb test
	Chair stand test
	Balance
Multi-activity tests	Short Physical Performance Battery (SPPB)
	Physical Performance Test
Site-specific	Loaded forward-reach test for chronic low back pain
	Knee range of motion
	Handgrip strength test
	Single leg hop test

Adapted from Taylor AM, Phillips K, Patel KV, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *Pain.* 2016;157:1836-50.
Note: References are in the text.

can be used. There is an important distinction between PROMs to assess emotional functioning compared to interview-based assessment designed to determine psychiatric diagnoses. The former depends on the patients' perception and reporting on their thinking and mood, whereas clinical interviews have a different purpose and require interpretation to arrive at a diagnosis.

For most clinical trials, PROs are used to assess emotional function as an outcome, a response induced by the treatment. As for physical functioning, emotional functioning and distress can be assessed by general measures or disease specific or population-specific measures. In the assessment of patients experiencing pain, the most frequent psychological constructs include anxiety and depression. General measure for anxiety include the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS),[31] State-Trait Anxiety Inventory (STAI),[128] and Generalized Anxiety Disorder (GAD-7),[32] and for depression, the Beck Depression Inventory (BDI),[129] and Public Health Questionnaires PHQ-9[130] and PHQ-4.[131,132] The emotional components of pain can also be assessed using the mental health component of the SF-36.[35] More specific measures include the Pain Anxiety Symptoms Scale (PASS-20),[133] Tampa Scale of Kinesio-Phobia (fear of movement),[134] fear-avoidance beliefs questionnaire (FABQ),[135] and Geriatric Depression Scale (GDS) (Table 84.5).[136]

Patients' Beliefs, Expectations, and Coping

Although not specifically recommended as core outcome measures of emotional functioning and patients cognitions (e.g. attitudes, beliefs, and expectations) are important in understanding patients/experience of pain and may mediate or moderate treatment outcomes. Some Instruments that measure attitudes and beliefs include the Pain Beliefs Questionnaire[137] Pain Beliefs and Perceptions Inventory (PBPI),[138] and Survey of Pain Attitudes (SOPA).[139] The chronic pain coping inventory (CPCI),[140] Coping Strategies Questionnaire (CSQ),[141] and Vanderbilt Pain Management Inventory (VPMI)[142]

TABLE 84.5 Selected Measures on Emotional Functioning for Use in Chronic Pain Studies

Sub-Domain	Measures
Anxiety	Beck Anxiety Inventory (BPI)
	Generalized Anxiety Disorder-7 (GAD-7)
	Pain Anxiety Symptoms Scale (PASS)
	State-Trait Anxiety Inventory (STAI)
Depression	Beck Depression Inventory (BDI)
	Beck Depression Inventory-II (BDI-II)
	Screening Version
	Older adult version
	Geriatric Depression Scale (GDS)
	Patient Health Questionnaire (PHQ)-Depression
Combination	Hospital Anxiety and Depression Scale (HADS)
	Public Health Questionnaire (PHQ)
	(PHQ-4)

Note: References are in the text.

are measures that evaluate coping strategies while the Catastrophizing Scale[143] and Pain Catastrophizing Scale[144] assess patients' catastrophizing. Finally, the Pain Locus of Control[145] focuses on patients' perceptions of control (i.e. self, powerful others, chance), while the Pain Self-Efficacy Scale[146] and the Chronic Pain Self-Efficacy Scale[147] assess the patients' perception of self-efficacy for controlling pain and their lives more generally. Several short-forms of these questionnaires have been developed and may be useful to reduce patient burden, e.g. pain catastrophizing,[148] pain self-efficacy,[146] and coping.[149]

Several general comprehensive measures evaluate pain, and physical and emotional functioning.[114] These include the BPI short form,[150] and MPI[67] for pain. For general health and interference of pain with functional activities and to some extent, SF-36,[36] SIP,[106] Nottingham Health Profile,[151] and PROMIS-29.[152] A very brief measure based on the BPI includes three questions, designed to cover key outcomes is the PEG.[153] The domains covered, each with a single item in the PEG, include average Pain, interference with Enjoyment of life, and interference with General activity, have the advantage of efficiency. It has been used in primary care settings. In addition to these general measures, there are a large number of comprehensive disease specific measures have been published, e.g. FIQ-R,[113] NDI,[111] and WOMAC (see Table 84.4).[75]

Measures in the Elderly and Patients With Cognitive Impairment

PROMs depend on the ability of the patient to respond to verbal questions. This creates unique problems for those patients who cannot respond to such inquiries. Assessment tools have been developed for the elderly and adults with cognitive impairment. Geriatric Pain Measure,[154] Pain Assessment in Advanced Dementia (PAINAD),[155] Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC),[156,157] and DOLOPLUS-2,[158] and the Pain Assessment in Impaired Cognition Scale (PAIC15).[159] These measures are discussed in Chapter 43 (Pediatric Chronic Pain Management) and 79 (Pain Evaluation and Management in Patients With Limited Ability to Communicate Because of Dementia). Similarly, measures are needed for neonates, infants, and young children. These are discussed later in this chapter. Complete psychological assessment is discussed in Chapter 22.

Domains and Measures in Acute and Chronic Pediatric Pain Clinical Trials

We combined the core domains for acute and chronic pain clinical trials for use in pediatrics for easier discussion and referral to the outcome measures. We will address acute pain first since, in contrast to adult studies, many of the pediatric recommended measures that have been used in acute pain trials have also been included in chronic pain trials.

It is important to acknowledge that selection of specific outcome measures in pediatrics is a daunting task that involves complex decision making and the selection of measures that are appropriate for the age and developmental status of the patients included in the study. We describe a wide range of assessment tools (i.e. PROMs, surrogate, physiologic) for the set of outcome domains recommended, each with advantages and disadvantages, that have been developed and used to assess the important outcome domains across developmental stages in this section. Many of the measures discussed are applicable across types of pain and various contexts. However, we also note several that are disease specific (e.g. migraine, juvenile rheumatoid arthritis) and context specific (e.g. postoperative, procedural, home, emergency department).

One of the most challenging concerns with pediatric pain assessment is that because many children are too young or developmentally immature to communicate their level of pain verbally,[160] we rely on the observer (e.g. parent, nurse) as a proxy to make an assessment. However, observers can over or underestimate children's pain[161,162] and can be influenced by their own beliefs, concerns, emotions, and contextual factors.[163] Ideally, a patient's own personal assessment of his or her pain is the gold standard, but validated observation and surrogate-reported scales can assist in both clinical decision making and research when self-report is limited (see below). Note that similar concerns apply when adults have limited or impaired ability to communicate.

For pediatric postoperative pain management, pedIMMPACT was developed.[3] Specifically, pedIMMPACT recommended pain intensity, physical functioning, emotional functioning, symptoms and AEs, and global judgment of satisfaction with treatment as preferred outcomes domains. These domains are slightly different from IMMPACT in that they did not incorporate satisfaction in the domain of patients' ratings of global improvement. According to pedIMMPACT, for chronic and recurrent pain, pediatric clinical trials, investigators should consider adding three additional outcomes to those recommended for acute pain trials, namely, role functioning, sleep, and economic factors. IMMPACT recommended that role functioning and sleep should be considered secondary outcomes and did not consider economic factors as a relevant outcome domain in adult clinical outcome studies.

For children, developmental stage and age are essential considerations in selecting measures to assess the outcome domains. Thus pedIMMPACT suggests measures that would be appropriate for different age cohorts.

For *self-report measures* of acute pain intensity in clinical trials and adolescents, pedIMMPACT recommended the Poker Chip Tool[164] for children aged three to four years of age for procedure-related and postoperative pain; the Faces Pain Scale Revised (FPS-R)[165] for ages four to 12 years for procedure-related, postoperative, and disease-related pain; and the VAS[166] for ages eight and above for procedure-related and postoperative pain. There are no validated self-reported pain scales for children under the age of three as many will not accurately self-report their pain. Thus for neonates and infants, assessment must be based on observation and estimation by surrogates.

The Poker Chip Tool consists of a set of four red plastic poker chips, each representing a "piece of hurt." In this scale, "hurt" is included as a proxy for "pain." The child chooses "how many pieces of hurt" they have. Children without pain have no pieces of hurt. The first chip represents "a little hurt," the second indicates "a little more hurt," and the fourth chip equals the "most hurt you could ever have." As such, scoring is from zero to four.[164] The FPS-R consists of six gender-neutral line drawings of faces that are scored from zero to ten.[165] The faces from left to right show no pain, increasing to more pain, and finally ends at very much pain. The patient then points to a face on the scale to represent their level of pain. The faces are meant to represent how a child feels inside, not how their actual face looks to the providers. The Wong-Baker FACES pain scale consists of six hand-drawn faces that range from smiling to crying.[167] The faces represent "no hurt" to "hurts worst," and the scale is scored from zero to five. The Oucher combines two separate scales: the photographic faces scale and a 0-100 mm vertical NRS. The photographic faces scale consists of six photographs of culturally sensitive faces (i.e. Caucasian, Afro-American, and Hispanic) that are scored from zero to five. The adjacent vertical NRS is scored from zero to 100.[168,169]

There is not complete agreement as to the types of pain assessment scales to use in pediatrics. PedIMMPACT recommended the use of the VAS and not the NRS because of the paucity of psychometric studies with NRS in pediatrics. The color analog scale (CAS) used gradations of color, area, and length to enable children to concretely identify variations in pain intensity.[169,170] The measure is pocket sized (10 cm in length) with gradations from small and white to wider and deep red reflecting increases in pain intensity. In the original CAS, children were asked to move a slider along the length of the CAS to indicate how much pain they have. The back of the measure has a corresponding zero to ten NRS to determine a number representing the child's pain.

A group of other investigators advocated for the use of self-report measures for the evaluation of pain when possible.[168,169] They noted that observer reports or behavioral observations are limited and may not be in agreement with the child's self-report as parents tend to underestimate or overestimate their child's pain. The group reviewed the psychometric properties, interpretability, and feasibility of self-report pain intensity measures. They noted that several self-report measures fulfilled the criteria of "well-established assessment."[171] These include the NRS (NRS-11), VAS, CAS, FPS-R, and original FPS, FACES, pieces of hurt/poker chip tool, Oucher photographic and numeric scales.[168,169] In contrast to pedIMMPACT, these investigators recommended the NRS-11 and the VAS across all types of pain for children six years and older.[169] Similar to pedIMMPACT,[3] they recommended the pieces of hurt tool for acute procedure-related postoperative pain in children between three and four years of age (with a behavioral observational measures as a secondary outcome); the FPS-R for acute procedure-related postoperative and disease-related pain in children four and 12 years of age; and the VAS for acute procedure-related postoperative and disease-related pain in children over eight years of age and adolescents, with the FPS-R as a secondary measure with the VAS for children between eight and 12 years.[168]

For *observational measures* of acute pain intensity from procedural and postoperative pain, pedIMMPACT recommended several tools for children one year and above. These include the Face, Legs, Arms, Cry, Consolability (FLACC),[172] the Children's Hospital of Eastern Ontario Pain scale (CHEOPS),[173] the Parents' Postoperative Measure (PPM)[174] for postoperative pain measure at home, and the COMFORT Scale[175] for children on a ventilator or in critical care. The Toddler-Preschooler Postoperative Pain Scale (TPPPS)[176] is recommended for postoperative pain in children aged one to five years.

The FLACC scale is a five item scale scoring the face (F), legs (L), activity (A), cry (C), and consolability (C), each with a range of zero to two.[172] The scale is scored in a range of zero to ten, with zero representing no pain. The revised FLACC scale incorporates additional observable behaviors to improve validity in children with cognitive impairment. Given its validation in a wide range of patients and its ease of use, it is a helpful tool for patients who cannot self-report.

The CHEOPS scale rates six behaviors: cry, facial expression, verbal responses, torso position, touch, and leg position.[173] The scale is anywhere from zero to three, depending on the specific behavior. The minimum score is four (no pain), and the maximum score is 13 (worst pain).

The PPM is a 15-item observation scale where parents report on changes from their children's usual behavior. The number of items parents have circled "Yes" are summed for a total score out of 15. A score of at least six out of 15 signifies clinically significant pain.[174]

The COMFORT scale combines observation and physiologic signs. It measures alertness, calmness/agitation, respiration, physical movement, blood pressure changes, heart rate changes, muscle tone, and facial tension. Total scores can range between eight and 40. A score of 17-26 generally indicates adequate sedation and pain control.[175] Because of the complexity of measuring blood pressure and heart rate, this scale is used primarily for patients in a critical care setting.

The TPPPS is an observational scale specifically only for children aged one to five years old.[176] The TPPPS consists of seven items divided among three pain behavior categories: (1) vocal pain expression, (2) facial pain expression, and (3) bodily pain expression. The seven pain behavior items were scored as "one" if the behavior(s) is present during a five rain observation interval and as "zero" if the behavior(s) is not present. Scores on the scale range from zero to seven. A modified TPPPS was noted to be a suitable assessment tool of pain in children who presented in an accident and emergency department.[177]

For children with intellectual disabilities, there is the Non-Communicating Children's Pain Checklist-Postoperative Version (NCCPC-PV).[178] It included vocal, social, facial, activity, body and limbs, and physiologic signs on a range of zero to three. A total score of seven or more indicates a child has pain. A total score of six or less indicates a child does not have pain. The tools mentioned above are discussed in Chapter 28.

For pediatric chronic pain trials, pedIMMPACT recommends the same self-report measures employed in acute pain studies. The number of pain-free days or days when pain reaches a certain level (e.g. three on a five point scale may also be noted).[3] The same tools

for assessing patient satisfaction and symptoms and AEs in acute pain are recommended.

There are no validated measures for physical recovery for acute pain in children.[3] Instead, the time to ambulation, time to resumption of swallowing, oral intake, time out of bed, time to ambulation, and time to normal spirometry have been recommended by the group. In addition, the IMMPACT group recommended the adolescent, pediatric pain tool[179] for emotional response; the facial affective scale for measuring the affective component of pain in patients eight years or older;[3] the Procedure Behavior Check List (PBCL);[180] or the Procedure Behavioral Rating Scale Revised (PBRS-R)[181] for evaluation of behavioral distress during procedures. The different presentations of global ratings of satisfaction do not appear to affect the response. For children below eight, proxy ratings by parents are advised. Evaluation of economic factors involves the assessment of both direct and indirect costs of the treatment.

For pediatric chronic pain studies, school age children and adolescents' assessment of physical functioning can be evaluated by the Functional Disability Inventory,[13,182] while PedsQL is utilized in children less than seven years, although it can be deployed in children two to 18 years old.[183] In addition to physical functioning, the PedsQL also determines emotional, social, and school functioning. As emotional functioning refers to depression and anxiety, these domains can be appraised by the Children's Depression Inventory for ages seven to 17 years and the revised Child Anxiety and Depression.[184]

For role functioning, the following measures can be evaluated: PedMIDAS for headache in children six to 18 years old;[185] school attendance for school age children; and the PedsQL across the pediatric and adolescent age-span. While sleep disruption is common in children with pain, the pedIMMPACT group does not recommend a specific tool. Finally, the group acknowledged the difficulty in assessing economic factors in children.

Additional measures not discussed by the pedIMMPACT group include the Children's Comprehensive Pain Questionnaire for school age and adolescent children,[186] and the pain behavior observation method for children with juvenile rheumatoid arthritis.[187] To evaluate anxiety, tools include the Children's Anxiety Sensitivity Index (CASI),[188] Multidimensional Anxiety Scale for Children (MASC),[189] and the revised children's manifest anxiety scale.[190] Self-report questionnaires for anxiety include the Self-report for Child Anxiety Related Disorders (SCARED)[191] and the Spence Children's Anxiety Scale.[192] The child's Coping abilities can be assessed by the Pain Coping Questionnaire (PCS),[193] Pain Response Inventory (PRI),[194] or the Pain Catastrophizing Scale for Children (PCS-C).[195] These measures are discussed in Chapter 43.

Patient Satisfaction

Although not traditionally considered an outcome in pain clinical trials, more recently, patient satisfaction with treatment has received growing attention and deserves to be included as an important outcome. Patient satisfaction is a barometer used by many hospitals to measure success and drives infrastructural changes.[196] The determinants of patient satisfaction are either patient-, provider-, and process-related.[197,198] Patient-related factors include physical and psychological health, expectations, and sociodemographic factors. The social and personal characteristics encompass age, race, gender, culture, social class, education, marital status, occupation, and income. Satisfaction is increased when the healthcare matches up to the patient's expectations. Provider-associated considerations include competence (perceived versus observed) and verbal and non-verbal interactions with the patient. Empathy, length of the provider's visit, and the amount of information given influence patient satisfaction. In addition, ancillary services, accessibility and convenience, cost, and bureaucratic and environmental factors, and organization of health care are process-related features.[197] Increased accessibility, shorter waiting times, and availability of the provider naturally improve patient satisfaction.

Patient satisfaction in acute pain management encompasses satisfaction with the process itself (i.e. the collective effort to achieve analgesia) and the outcome (i.e. the success of the pain regimen).[199] Although overlap exists, the two components should be viewed as separate entities.[196] Although a patient could receive inadequate pain control, he or she may be thankful for all information provided, and the providers attempt to ensure optimal analgesia. Conversely, a patient with minimal postoperative pain could be dissatisfied because of preconceived expectations and to his or her lack of involvement in the decision making process. For example, published studies noted that satisfaction was dependent not only on anesthetic outcome but also on how patients were approached and how the information was relayed.[200,201] The results showed that process-related factors (e.g. participation in decisional process) are just as important as outcome-based parameters (i.e. pain intensity) in ensuring patient satisfaction.

The type of treatment can also affect patient satisfaction. After total joint surgery, joint function, hip instability, leg length equality, and self-care are major determinants.[202,203] Range of motion, improvement in strength, and ability to perform activities of daily living are important after hand surgery.[204] Appearance after cosmetic surgery following a breast cancer operation determines patient satisfaction.[205] In these surgical publications, patient education, shared decision making, length of follow up, duration of waiting time, state of the facility, and quality of food also significantly affect patient satisfaction.[202–204] The surgeon's empathy, rather than duration of visit, positively influenced the patients' satisfaction.[206]

Satisfaction also depends on patient-related factors that can escape medical control.[197] In a recent observational study, patient-related sociodemographic variables such as male gender, older age, and higher education level were associated with increased satisfaction scores after anesthesia.[207] A cross-sectional analysis of patients undergoing non-obstetric surgery in the United Kingdom identified younger age, female sex, obesity, history of stroke, neuropathic pain, and long-term opioid use constituted non-modifiable parameters associated with severe discomfort after surgery.[208]

Tools to measure patient satisfaction include user-friendly questionnaires to validated measurement tools. Simple measurement methods include satisfaction scores presented in the NRS or verbal descriptor scales. However, the reliability of these scales is questionable since they cannot capture the manifold nature of satisfaction.[199] The patient global impression of change (PGIC),[209] a very popular tool and recommended by IMMPACT, has been utilized to represent patient satisfaction. However, it does not assess satisfaction *per se.* Patients simply comment on their overall status and whether the latter has changed, worsened, or remained status quo. This scale does not capture the multidimensional and complex nature of satisfaction.[196]

Reliable setting-specific and procedure-related tools have been devised and validated to assess patient satisfaction and related to anesthetic management. These include the Iowa Satisfaction with Anesthesia Scale for monitored anesthesia care,[210] and the Scale of Patients' Perceptions of cardiac anesthesia services.[211] Sophisticated questionnaires developed for general non-cardiac anesthesia include the evaluation du vécu de l'anesthésie générale (EVAN-G)

questionnaire,[212] Leiden Perioperative Care Patient Satisfaction questionnaire (LPPSq),[200] patient satisfaction questionnaire for Anesthesia Care,[213] Patient Satisfaction with Perioperative Anesthetic Care questionnaire (PSPACq),[214] Anesthesiological Questionnaire (ANP),[215] and the Bauer questionnaire.[216] The EVAN-G questionnaire is designed for patients who had general anesthesia, whether inpatient or ambulatory. It consists of 26 questions pertaining to attention, privacy, information, pain, discomfort, waiting, and global impression.[212] The EVAN group recently developed a psychometrically sound satisfaction questionnaire for regional anesthesia.[217] The patient satisfaction questionnaire for anesthesia care, developed by investigators from Switzerland and Austria, contains items on information (and involvement in decision making) on care in the recovery room and pain management.[213] In contrast, the Bauer questionnaire includes ten anesthesia-related questions pertaining to discomfort (e.g. pain at surgical or injection site, sore throat, hoarseness, thirst, cold, shivering) and five questions pertaining to satisfaction with preoperative information, emergence from anesthesia, pain, and overall anesthesia care.[216] The five straightforward questions related to patient satisfaction explain the use of the Bauer questionnaire in a large cross-sectional study investigating the outcome of perioperative anesthesia in the United Kingdom.[208] The time required to complete the questionnaires usually ranges from 3 to 12 min.[218] Most tools are linguistically specific to the population for whom they were originally developed. While the EVAN questionnaires have English translations, the ANP and the perioperative anesthetic care questionnaire have not been translated in English and are specific to German and Taiwanese patients, respectively.

The previous questionnaires target patient satisfaction. In addition, there are validated multidimensional tools that include patient satisfaction as part of the overall assessment of pain management. These include the APS-POQ-R)[11] and the IPO questionnaire.[40] The APS-POQ-R was developed for QI audits of pain management, while the IPO, a modification of the APS-POQ-R, was designed for postoperative application. Both questionnaires include a question on patient participation in the therapeutic decisional process. We suggest that a tool to evaluate patient satisfaction should be included if these general measures are utilized in acute and chronic pain outcome studies.[39]

Summary and Conclusions

Pain is a biopsychosocial construct, and clinical trials on pain should reflect its multidimensional nature. It includes not only the intensity of the pain but also physical and emotional aspects. AEs are consequences of any treatment. Patient satisfaction reflects the interaction of all these domains. Measures that determine these domains and possess valid psychometric/clinometric properties have been identified in acute, postoperative, and chronic pain in adult and pediatric populations. Published clinical studies on chronic pain have utilized these measures and recommendations proposed by IMMPACT, while investigations in acute and postoperative pain have started to embrace the domains recommended by IMMPACT and APS-POQ-R. Outcome domains for acute and chronic pain in children, as proposed by pedIMMPaCT, are largely similar to those proposed for adults. In pediatric research, the age and developmental stage must be considered when selecting specific measures for the outcomes of interest. A large and growing list of both general and specific measures has been developed for adults and children. Investigators need to be cognizant of the basic psychometric/clinometric characteristics of all measures they consider. They also need to attend to the responsiveness of the measures to change and the normative samples on which the measures were developed to assure that the measure is appropriate for the sample to be included in the trial. Although we focused on measures that can be considered for use in clinical trials, many of the measures should be considered appropriate for use in clinical practice.

Key Points

- Pain is multidimensional and clinical trials on acute and chronic pain should reflect its multifaceted nature in the outcomes used to evaluate various interventions.
- IMMPACT recommended that six core domains should be considered in chronic pain clinical trials; (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; and (6) participant disposition (adherence to the treatment regimen and reasons for premature withdrawal from the trial).
- The selection of measures to assess the important outcomes in clinical trials should attend to the (1) reliability, (2) validity, (3) responsiveness, (4) availability of appropriate comparison groups and generalizability to the study sample, (5) patient burden, (6) appropriateness for the sample included in the study, and (7) the criteria for clinical significance.
- IMMPACT recommended measures appropriate for each of the above domains. Generic or disease specific measures with valid psychometric properties are available for low back pain, fibromyalgia, musculoskeletal and joint pain, neuropathic pain, and other chronic pain syndromes.
- NRS, VRS, and VAS are reliable, and all consistently show greater ability to detect improvement after treatment. However, IMMPACT recommended the 11-point NRS because of concerns raised about the ability of older populations to understand the use of VASs, and they can be difficult to use during telephone interviews and with handheld devices.
- The neuropathic pain measures determine the qualities and progress of the neuropathic pain syndrome and questionnaires that determine whether a pain syndrome consists mostly of neuropathic features.
- Most clinical trials on chronic pain included the domains recommended by IMMPACT, but studies on acute or postoperative pain have been less consistent in making use of IMMPACT and APS-POQ-R recommendations. Emotional functioning is the least studied domain in postoperative pain trials.
- The QoR tool for postoperative pain is the most commonly used multidimensional tool in perioperative pain studies. However, patient satisfaction should be investigated when using the QoR since it does not measure such outcomes.
- Clinical trials on pediatric acute and chronic pain should strive to include the same domains as in adult studies. The choice of measures for each domain should consider the age appropriateness and limitations posed by those whose ability to communicate are impaired.

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Ethical Issues in Pain Research

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There are numerous ethical considerations when conducting pain research with humans. In this chapter, we will briefly review the genesis and growth of research ethics as a field, often in response to historical examples of research misconduct. We then discuss ethical issues specific to the study of pain, including (1) how pain can affect an individual's ability to act autonomously, (2) unique risks of study participation for patients with pain, (3) justice concerns regarding participant selection and distributing the benefits and burdens of research, (4) the ethics of inducing pain for research purposes, (5) controversies over the use of placebos, (6) issues specific to studying pain in children, and (7) burgeoning considerations in the study of genetic and epigenetic phenomena related to pain. We recognize that any one of these issues may warrant an entire chapter, and as a result, our effort is to summarize issues rather than address them exhaustively.

Brief Historical Overview

The field of research ethics with human participants was borne out of numerous instances of research misconduct and scandal that have marred the legacy of medicine and science. During the Nazi regime, harmful and deadly experiments were conducted on concentration camp inmates to determine the conditions (and limits) under which military personnel could survive, testing medications and treatments, and carrying out eugenic ideals.[1] The Nuremberg Code was authored in 1947 by judges who presided over the trial of Nazi physicians, and this code laid the foundation for all subsequent research ethics declarations. It emphasized the protection of human research participants' rights through informed consent and the right to withdraw from research, as well as the duty of the investigator to act in participants' best interests.[2] Other research scandals that have informed the field of research ethics include the intentional infection of disabled children with Hepatitis A at the Willowbrook Institute in the 1950s,[3] the propagation and widespread distribution of an immortal cell line obtained without permission from Henrietta Lacks—a black woman dying of cervical cancer,[4] and the United States Public Health Service's "Tuskegee Study of Untreated Syphilis in the Negro Male," a forty-year observation during which men were not told the truth about the study's purpose, nor were they offered treatment when it became readily available.[5]

In 1964, the World Medical Association developed the Declaration of Helsinki, which outlines proper conduct for physicians who perform research. It has been revised multiple times and remains a key resource guiding the ethical conduct of research worldwide. The 1975 revision defined the need for oversight by an institutional review board (IRB) to protect human subjects, paralleling a similar requirement instituted in 1974 by the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the United States.[6]

That same commission authored the Belmont Report, published in 1979, which establishes respect for persons, beneficence, and justice as the ethical principles that must be considered and balanced in the research context.[7] Respect for persons encompasses two "convictions": that individuals should be allowed to act autonomously and that those with diminished autonomy are deserving of extra protection. Respect for persons underlies the requirement for informed consent in research participation. To act beneficently is to promote a person's wellbeing. In research, this duty requires that investigators thoroughly assess the potential benefits and harms of their study and try to maximize benefits and minimize harms to participants. Justice, in the words of the Belmont Report, focuses on "who ought to receive the benefits of research and bear its burdens?" Ethically conducted research must have a process for participant selection that does not take advantage of vulnerable or captive populations, and the findings from publicly funded research must benefit everyone, not a privileged minority. Freedman writes that ethical research should also be scientifically valid (thereby producing reliable and generalizable data) and be of use to society.[8]

The 2018 update to the United States Code of Federal Regulations governing human subjects research considers children, prisoners, individuals with impaired decision making capacity, and economically or educationally disadvantaged persons to be vulnerable populations. That is, these populations have constrained or limited autonomy and may be susceptible to coercion or undue influence.[9] IRBs are obligated to scrutinize research involving these populations to ensure that the benefits of research participation are not outweighed by potential harms. When research involving children does not hold the prospect of direct benefit, it may still be approved if it is considered to present "minimal risk" or a "minor increase over minimal risk" of harm to the child. For a study to be deemed "minimal risk," the probability and magnitude of harm or discomfort anticipated in the research "are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." This standard has been criticized because of its lack of specificity and potential for variable interpretation by individual IRBs; nonetheless, it remains the standard criterion employed to categorize research risks.[10,11]

Ethical Issues Specific to Pain Research

The experience of having pain may compromise a participant's ability to act autonomously and provide valid informed consent. Pain is noxious, and individuals' judgment may be ill-affected

by the immediate desire to make it stop. Included here is that pain may impair cognition,[12] and the ability to reason beyond the immediate goal of relief. Especially patients for whom pain has been poorly controlled, there may be a tendency to overestimate the potential benefits of an experimental therapy resulting in a biased assessment of the harm to benefit ratio.[13] Thus investigators have a heightened obligation to ensure that prospective participants can understand and reason with information pertinent to risks and benefits of study participation.

A crucial component of autonomous action is voluntariness; the potential research participant must be free to enroll in a study without experiencing overt or implicit coercion. The pain research context may threaten voluntariness in a few ways. For example, there is a risk that some individuals will feel compelled to enroll in a study that is presented by their healthcare provider to maintain the therapeutic relationship and be seen as a "good patient." Also, incentives offered by the research program may overtly exert influence on potential research participants. Incentives are intended to attract participants and compensate them for the time, effort, and discomfort that research may entail. However, when an incentive is disproportionate to the study burdens and is so enticing that the participant feels there is really no choice to be made, this is termed "undue influence" and is considered unethical. On a more subtle level, improved access to healthcare services only while "on study" could serve to unduly influence some potential participants to enroll. This issue is especially problematic in developing economies.

Investigators must minimize harm to research participants. Investigational pain therapies pose risks of an altogether different type than that typically experienced in other pharmacologic trials. Analgesic trials for short-term acute or post-procedural pain involve very limited administration of the study drug. However, for chronic pain, participants may receive the study drug over several days to weeks. If that medication is superior to contemporary therapies, it may be difficult for the participant to revert back. This issue is highlighted even more when the study drug promotes physical dependence (as in the case of opioids). There is an obligation to ensure ongoing followup beyond the scope of the trial.

Last, investigators must consider if the participants they plan to enroll are representative of the population to whom they ultimately hope to provide benefit. Clinical trials are often relatively narrow in defining inclusion criteria, and biases based on age, language, and sociocultural factors are far too common.[14] For example, vaso-occlusive episodes characteristic of sickle cell disease may be exceedingly painful and require potent analgesics for treatment. However, even fundamental research on analgesic medications (e.g. pharmacokinetic and pharmacodynamic studies) in this patient population was rare for many years.[15,16] The pediatric population has also been omitted from most analgesic trials, which will be discussed further below.

Ethics of Placebos

The long-standing method by which analgesics have been tested is by randomly assigning participants to receive the test drug or a placebo and then comparing mean pain scores (typically, a rating of pain intensity). The ethical concern is that those assigned to the control group are likely to experience pain until they receive rescue medications. This may be justified if there is true equipoise – that is, the researcher truly does not know if the test drug is superior to placebo. However, this is rarely the case with analgesics, and thus alternative study designs have been pursued.

Nagasako and Kalauokalani explicated these concerns drawing on lessons learned in psychiatry to make recommendations for the field of pain medicine.[17] Whether the use of placebo controls may be judged as ethical depends partly on the state of existing treatment (i.e. if existing treatments have been rigorously studied and shown to be effective, then new drugs may be compared against existing treatment, not placebo). However, if the best available therapy has not been rigorously established or the treatment effects vary significantly across a population, then for some participants, treatment with placebo would be no better than treatment with the "best available" therapy.

Another consideration is whether the condition under study can allow for the potential harms of placebos.[17] An individual exposed to a cold pressor stimulus (experimentally induced pain) would not experience significant harm if given a placebo. In contrast, a person who had undergone abdominal surgery could experience significant harm if given a sham epidural or a placebo instead of a parenteral analgesic.

It is also worth noting that placebo-controlled studies have merit. "Placebo concurrent control" is one of five study designs recommended in the United States federal regulations regarding controls in drug studies.[18] Randomized, double-blind, placebo-controlled trials minimize bias (both on the part of the investigator and the participant), provide an internal standard against which efficacy of the study drug can be measured, and provide the cleanest conditions for distinguishing adverse drug effects from effects of underlying disease.[19] Scientific validity can be considered an ethical principle, which lends support to the use of placebos.[8,17] Furthermore, one cannot ignore the profound clinical effects of a placebo. A review is well beyond the scope of this (see Chapter 17). However, any time one administers a drug, the clinical effect is the combined impact of the therapeutic effects of the drug and placebo, and often the latter is far greater than the former.[20] The placebo effect is so strong that it remains intact, even when patients know they are receiving a placebo.[21,22] How could one measure this profound effect without including a placebo control?

The Ethics of Laboratory Induced Pain in Humans

One may potentially learn a great deal about pain and its impact by inducing nociception experimentally and studying various correlates. Research involving experimentally induced pain enables us to study and manipulate different variables to understand relationships in ways not feasible in a naturalistic setting. We may better comprehend the trajectory of pain syndromes, the contributions of genetic, biologic, and psychological factors, and, ultimately, pain prevention, coping, and treatment. Despite the potential wealth of information that this type of research can produce, when one is intentionally inflicting pain on another human, ethical considerations, focused on how pain may be evoked in the laboratory, and the range of outcomes of interest to investigators, are paramount.

Pain may be induced through various means, including mechanical, temperature (heat and cold), ischemic, vibration, and electrical stimulation. Within experimentally induced pain studies, outcomes of interest may include (1) *pain threshold*, the lowest level of nociceptive stimulation the participant labels as painful; (2) *pain tolerance*, the maximum level of nociceptive stimulation the participant is willing to withstand; and (3) *pain responsiveness*, the participant's subjective, behavioral, or physiologic response to a defined or standardized nociceptive stimulus.

The risk-benefit ratio used to evaluate the ethical status of a given study in this arena depends on the nature of the pain being inflicted (including the specific stimulus itself, its intensity, and duration) and the presumed gains from obtaining the data. A thorough review of various means of inducing pain and the methodologies used in laboratory studies is beyond the scope of this chapter.[23,24] However, to meet ethical standards, certain common elements are universally important. For example, painful stimuli should be of the lowest intensity and the shortest duration needed to answer the research question. In addition, full informed consent is imperative, including the participants' right to withdraw from the study at any time without penalty.

In research involving laboratory-induced pain, attention to external validity is essential. Participants selected for research trials should be representative of the population to whom the results are to be generalized. For example, imagine the differences in pain tolerance that might be ascertained in a study conducted on military recruits versus college undergraduates versus a community sample of middle-aged adults. Without ensuring that a study's results will be generalizable to a target population, the benefit of the study is not obvious and potentially inherently unethical.

There is a long history and continues to be a growing body of literature supporting the clinical relevance and application of laboratory induced pain.[25,26] For example, by studying conditioned pain-modulation (formerly called diffuse noxious inhibitory controls, DNIC) using Quantitative Sensory Testing (QST), one can predict elements of patients' acute, postoperative, and chronic pain responses.[27] As clinical applications of experimentally induced pain expand, it is still important to maintain the same ethical framework of gaining the needed information while minimizing patients' exposure to noxious stimuli.

In conducting laboratory pain studies with minors who are incapable of providing informed consent, even more rigorous standards must apply. As study participation is of no immediate benefit to the child participant, the value of the research must be apparent, the child's informed *assent* is essential, and the right to withdraw should be made clear to the child participant and the child's parents or guardians. This field has clearly evolved. In 1986, a study involving pain thresholds in pediatric patients led to an initial uproar within the IRB, and they demanded a personal appearance by the investigators. Once the IRB learned that the methods included nothing more than inflating a blood pressure cuff until the child or guardians first labeled the circumferential pressure as pain, and using a simple pressure algometer on the index finger until the child first labeled the stimulus as pain, they approved the study with no further ado.[28] Since then, many studies with children have gone on to include pain tolerance, principally through a cold pressor paradigm,[24,29] and pain responses, and their correlates through QST methodology.[30]

The majority of early trials involving experimentally induced pain were with healthy children. However, much may be learned about individual differences, sociocultural elements, and contextual factors that influence clinical pain syndromes, by including participants with chronic pain or other comorbidities. In a recent review of emerging trends in pediatric and adolescent pain research, Wilson and colleagues discussed studies focused on aspects of conditioned pain modulation, temporal summation, neurophysiologic measures, condition-specific protocols, and psychological factors. They then turned an eye to future research, specifically on those at risk for or presenting with chronic pain problems.[30] They bring up ethical issues, as described below, regarding the cold pressor test. However, these considerations would be relevant for other methods of inducing pain in the laboratory with minors and adult volunteers.

von Baeyer and colleagues defined some key elements to pursuing this cold pressor research in children.[29] They posited that while generally one should avoid inflicting pain on children, there may be a great deal to be learned about pain processing by conducting such studies. Ethical concerns with minors as well as adults may be addressed if the paradigm (1) is demonstrated to be a valid means of gaining the needed information, (2) is the only means by which the information could be obtained, (3) involves no tissue damage or significant psychological distress, and (4) uses the least possible amount of stimulation to answer the study question. Risk may be minimized by providing participants control over the situation, such as discontinuing participation and controlling the stimulus to have it withdrawn to minimize exposure to high levels of discomfort. They then go on to provide specific methodologic recommendations to minimize risk.[29]

Birnie et al. examined Although this paper was specifically focused on children,these same ethical and methodological considerations may be applied to adults as well. ethical concerns and acceptability of the cold pressor paradigm from the perspective of researchers, parents, and children.[24] Using a survey of research professionals and questionnaires directed to children who participated in cold pressor studies and their parents, the authors found that for most such studies, full IRB processes were required. In these studies, adverse events are extremely rare, and overall experiences by all were positive. Thus with mindfulness of risk and appropriate safeguards in place, ethical concerns about laboratory -induced pain in children may be addressed.

Clinical Trials in Minors

The traditional analgesic trial for acute pain is a double-blind, randomized, placebo-controlled trial. A relatively straightforward pain model, such as third molar extraction or bunionectomy post-procedure pain, is used to test a drug against a placebo, typically relying on pain intensity scores as the dependent variable. Thus individuals agree to participate for the benefit of payment, recognizing that there may be a period of under- or untreated pain before they receive rescue. However, it is unethical to seek such consent from a minor as they are deemed incapable of conducting such a risk-benefit analysis for themselves.[31] Several organizations have weighed in to protect the rights of children participating in such clinical trials.[32]

Few drugs are adequately studied and labeled for use in children. Prior to recent innovation, only about 20% of drugs that were approved by the United States Food and Drug Administration (FDA) included labeling for pediatric use.[33] Therefore pediatric providers have had to face an unfortunate choice with regard to treating pain: They either prescribe a drug "off label" with inadequate data on safety and efficacy or leave pain untreated, causing significant suffering and potential for long-term deleterious effects. Through federal legislation that incentivized (Best Pharmaceuticals for Children's Act; BPCA) or required (Pediatric Research Equity Act; PREA) pediatric drug trials, the situation has improved over the past two decades. As of March 2020, 791 new pediatric studies resulted in various labeling changes, either supporting or not supporting specific medication use in pediatric age groups.[34] However, only six moieties were shown to be safe and effective, specifically for pain indications in children under age 11 years.

Given the changing landscape of pediatric research, the FDA convened an expert panel in 2009 to address the methodologic and ethical concerns inherent to pursuing analgesic trials in children

and to give explicit consideration to the practice of extrapolating from adult trials to predict drug efficacy in children.[35] Using the "not greater than minimal risk" standard described above, it was clear that it would be unethical to enroll infants and children in placebo-controlled trials, as there was the potential for them to experience un- or under-treated pain. The panel discussed other methodologies, especially immediate rescue paradigms, where nurses or parents provided analgesia, and the principal outcome is shifted from pain scores to analgesic usage. Similarly, rather than relying only on placebo-controlled trials, non-inferiority trials using various analgesic medications have shown validity.[36]

Studying pain and analgesia in neonates is particularly challenging. Until the mid-1980s, many believed that newborns—especially premature newborns—did not experience significant pain, and if they did, it would have no lasting effects. With this mindset, there was no need for analgesic trials. However, research has shown that even the youngest premature infants demonstrate hormonal and metabolic changes in response to nociception, and there are significant short and long term sequelae of pain experiences in this age group.[37] Fortunately, perspectives on the need for analgesic trials involving neonates and infants have begun to shift, and various issues for consideration and methods to conduct such research have been espoused.[38]

The use of control groups in studies of infants remains an outstanding issue. As the field recognized that infants experience pain and that methods to relieve pain exist, questions arose about whether it is ethical to include a "no treatment" condition in a neonatal study when evidence of effective treatments was available.[39] Pain researchers should know enough about the field to recognize the unacceptability of exposing an infant to untreated pain. However, evidence indicates that this concern has not been shared universally among the research community; a review published in 2016 found that in clinical trials of analgesics for painful procedures, 64 percent of babies in the control groups received either placebo or no treatment.[40] Regardless of whether researchers are from within or outside of the pain medicine field, outdated local standards of care should not be tolerated as a control group for studies of pain in children, as those standards are often inadequate.[41]

As children mature, they develop the capacity to understand medical information and become increasingly able to provide meaningful assent or dissent for medical interventions and research. The United States Code of Federal Regulations defines assent as "a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent." Each potentially approvable category of research involving children includes the stipulation that "adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians." Precisely when and how investigators should seek assent, however, remains vague.

Sterling and Walco have discussed the complicated interactions of child development and notions of what is necessary for valid consent/assent, and they question the soundness of stipulations in the federal guidelines that suggest that some research may be deemed so important that child dissent may be ignored.[42] They argue that investigators and IRBs must take responsibility for a customized approach to assent for the children who may become research participants. They also call for a formal study to establish the elements that define assent, as has been defined for informed consent, and empirical investigations of how best to address these elements in children of various ages and developmental stages.

Ethical Issues in Genomic Approaches to Understanding Pain

As is the case in so many areas of medicine, genomics research has the potential to improve our understanding of certain pain conditions. Many genes have been identified that have a role in the experience of pain and its treatment, such as genes responsible for neurotransmitter signaling, drug metabolism, and pain perception and modulation.[43]

However, with this potential come additional ethical concerns. Inherent to genome sequencing is the generation of large amounts of data for which researchers need to have a specific plan for protection and usage. Tissue samples and genomic information may be saved in a central repository for subsequent study. Researchers are obligated to ensure the data are secure, given the highly sensitive nature of genomic data and potential for re-identifying individuals through their genetic information. Several provocative questions emerge when considering genomic studies: What (if any) results will be returned to the research participant? Will researchers report only on the genomic region of interest for the study, or will they report more broadly? What will be the plan for disclosing pathologic genes or mutations found incidentally? What if the findings have implications for family members? For these questions, eliciting the participants' and families' preferences in advance of sample collection is crucial. Clearly, not all participants are comfortable with biobanking or broad data sharing. For a more detailed discussion of ethical issues arising in pediatric genomic research, see Rotz and Kodish.[44]

A major focus of the 2018 revisions to the United States CFR "Common Rule" was the handling of consent for genomic research. The common rule allows for "broad consent," in which a participant provides prospective consent for the unspecified future use of identifiable biospecimens and private data.

Last, equity and inclusion are important considerations when banking specimens and genomic information. Is there over-or under-representations of particular ethnic groups? What harms could come from the use of these data in the future? A helpful framework when considering genomic research involving minority communities has been presented by Claw et al. previously.[45] Moreover, all of these questions are of great significance, and the field is progressing so rapidly that new ethical challenges continue to emerge before we have clarity on some of those already posed.

Conclusion

Researchers in the field of pain must adhere to the same ethical standards as any other medical researcher and attend to a series of elements unique to the study of pain. Participants with pain may be uniquely vulnerable. Trial designs need to be evaluated for the potential harm to both individuals and populations. As technology advances, new questions of what is "ethical" will continue to emerge. Our ultimate aim is to relieve suffering, and studies must be designed to answer the research question while exposing participants to as minimal discomfort as possible. While designing ethically sound research protocols takes careful consideration, investigations that have been conducted with the help of voluntary participants, that have employed fair selection processes, and that have respected the wellbeing of participants will produce valid results and promote trust in the scientific enterprise.

Key Points

- Essential principles of research ethics include respect for persons, beneficence, and justice. In addition, research methods must be valid and produce results of scientific value to justify the risks to which research participants are exposed.
- Ethical challenges particular to research in the field of pain medicine include:
  - Pain may compromise participants' ability to act autonomously.
  - Potential participants' willingness to volunteer may be compromised by situations in which their healthcare provider is also a study investigator or if participants' actual or perceived access to health care and pain relief is contingent upon study participation.
  - Unique risks of participation in analgesic trials include uncontrolled pain during the trial (especially if assigned to a placebo arm), uncontrolled pain when coming off of study medications, and the development of tolerance and the experience of withdrawal, for certain classes of medications.
- There are ethical arguments for and against the use of placebos in pain research. Placebo designs can minimize bias, provide a standard against which treatment efficacy can be measured, and establish conditions for distinguishing adverse treatment drug effects from effects of underlying disease; these features are consistent with the principle of scientific validity. However, the use of placebos may violate principles of beneficence and justice when the research involves participants with compromised autonomy or is conducted in an area for which a broadly available and efficacious standard of care already exists.
- Studies involving laboratory-induced pain must attend to the following issues:
  - The study design and participant population must ensure external validity and generalizability of the results.
  - The study's methods must be a valid and necessary means of gaining the needed information.
  - The process of inducing pain must not cause tissue damage or significant psychological distress.
  - The least possible amount of stimulation should be used to answer the study question.
- Although it is widely understood that infants experience pain, and there is much to be learned about the safest and most effective ways of providing comfort and analgesia in this population, studies continue to appear in the literature that have not adequately provided rescue analgesia or comfort measures for infants in placebo or control groups.
- Genomic approaches to the study of pain introduce several ethical concerns surrounding the immense amount of data that can be generated, the potential to re-identify participants based upon genomic information, and the implications that population-level genomic information can have on cultural narratives, biases, and access to healthcare services.

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Treatment Development: Directions and Areas in Need of Investigation

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Introduction

Over the past decades, numerous advances have been made in pain medicine. Despite these advances, there are many gaps in our knowledge of the treatments currently available. We describe potential areas for investigation, including perioperative pain management, pharmacologic, interventional, and non-interventional chronic pain management.

Perioperative Pain Management

Significant progress in the management of perioperative pain has been made over the past two decades. Increased awareness of the treatment of postoperative pain, improved analgesic techniques, and new analgesic agents have contributed to improvements in its management. Despite these advances, many challenges remain to improve the quality of pain control.

Enhanced Recovery Pathways

Enhanced recovery programs (ERPs) for surgical patients may reduce variation in care and improve perioperative outcomes through the development and implementation of standardized, evidence-based perioperative pathways.[1,2] Multimodal analgesia incorporating primarily non-opioid agents and techniques (e.g. regional anesthesia/analgesia, nonsteroidal anti-inflammatory agents, acetaminophen, gabapentinoids, and local anesthetics) to minimize perioperative opioid use and side effects is a central tenet of ERP programs.[3] Although initial ERP programs focused on colorectal surgery, they have been increasingly adopted for a broad range of complex surgical procedures. The available literature indicates that implementing ERP pathways will result in decreases in hospital length of stay (LOS)/costs and perioperative morbidity, including lower risk of pulmonary, infectious, and gastrointestinal complications.[4–6] ERPs have received increased interest in the United States over the past decade, in part because of the increased emphasis by payers on quality-based reimbursement and bundled payments.

As ERP programs become a more routine part of surgical care, several areas require further investigation. For example, the optimal analgesic combination for ERP programs is uncertain. There has been increased scrutiny regarding the use of analgesics commonly used in most ERP pathways. Gabapentinoids are an integral part of most multimodal analgesic regimens postoperatively, and when administered as a single dose preoperatively, they have been shown to decrease pain and nausea/vomiting. However, recent literature raises concerns about the efficacy and perioperative respiratory depressant effects of gabapentinoids.[7,8] The United States Food & Drug Administration (FDA) officially released new warnings for gabapentinoids regarding the risk of respiratory depression.[9] However, the precise role of gabapentinoids in perioperative multimodal analgesia needs to be elucidated.

The use of regional anesthesia/analgesic techniques is an integral part of most ERP pathways because the benefits of its use (minimization of opioids, superior analgesia) facilitate the ERP goals of promoting earlier patient recovery. However, there is a paucity of literature examining the precise contributions of regional anesthesia/analgesia (vs. none) within the context of an ERP pathway.

Increased compliance with process measures directly influenced by the anesthesiologists, including the use of multimodal analgesia, and in conjunction with a formal anesthesia protocol, such as an ERP pathway, is associated with reduced LOS. In one study, patients who received high compliance (vs. low compliance) in ERP pathways had a significantly lower LOS, and multivariable regression indicated that utilization of multimodal analgesia and strict adherence to a postoperative opioid administration protocol for breakthrough pain were independently associated with reduced LOS.[4]

Although the use of ERP pathways can minimize postoperative opioid use, perioperative opioid minimization does not routinely translate into decreased prescriptions for opioids upon discharge. For example, in one study, implementation of an ERP colorectal pathway did not result in significantly lower opioid prescriptions at discharge even though these patients had a combination of low discharge pain scores, no preoperative opioid use, and low morphine milligram equivalent consumption before discharge.[10] Further studies are needed to determine how to modify opioid prescription practices on discharge after surgery in an attempt to continue opioid minimization after hospital discharge.

Chronic Post-surgical Pain

Chronic post-surgical pain (CPSP) is a potentially debilitating postoperative complication that may have a significant impact on activities of daily living and decrease the quality of life in adults[11]

and pediatric surgical patients.[12] Large observational trials suggest that CPSP may occur in 10% of patients postoperatively and may be severe in 1 of 100 patients.[13,14] A neuropathic component that predicts more severe CPSP is present in a significant portion of patients with CPSP as a systematic review of CPSP noted the presence in 6% of patients after total hip/knee arthroplasty and 68% of patients after thoracic and breast surgeries.[15]

There are many risk factors for the development of CPSP. Preoperative pain and psychological vulnerability (i.e. anxiety and catastrophizing) are two of the most important preoperative risk factors for the development of CPSP.[14] Intraoperatively, surgical technique has also been shown to be an important risk factor for the development of CPSP, primarily because of intraoperative nerve damage.[16] In addition, the intensity of acute pain postoperatively has been shown to be associated with the development of CPSP.[14] Although these risk factors are strongly associated with the development of CPSP, there is no causal relationship between any individual risk factor and the development of CPSP, such that decreasing/attenuating the severity of risk factors would automatically result in a decrease in the incidence or severity of CPSP.

Although we have improved our understanding of CPSP over the past decades, we still lack solid evidence for the prevention and treatment of CPSP in part because many studies have significant methodologic issues.[17] Well-designed prospective trials for various modalities for the prevention and treatment of CPSP are needed as most available studies on CPSP are based on retrospective observational data. Moreover, meta-analyses of treatment modalities for either the prevention or treatment of CPSP rarely have sufficient meaningful data to perform a subgroup analysis for individual CPSP syndromes. One interesting future area of investigation is the trajectory of acute postoperative pain (i.e. the slope or resolution of pain) that may be important in predicting the development of CPSP.[14,18]

Treatment strategies for CPSP can be grouped into pre-, intra-, and postoperative interventions. These strategies are described below.

Preoperative Considerations

Preoperative Opioid Optimization

The incidence of chronic opioid use by patients prior to surgery has been estimated to be approximately 9%.[19,20] The presence of opioid use prior to surgery has been associated with worse economic outcomes, including longer length of hospital stay, increased incidence of hospital readmission, increased financial costs, and lower incidence of return to work.[20,21] In addition, observational studies suggest that the preoperative use of opioids is correlated with an increase in postoperative patient mortality and morbidity, including higher surgical site infection rates, higher rates of reoperations, constipation, neurologic complications, acute renal failure, venous thromboembolism, and subsequent opioid abuse.[22–24]

There is relatively little high quality data in preoperative opioid optimization despite the increased interest in weaning opioids prior to surgery. Future studies should attempt to confirm the correlation between preoperative opioid use and increased perioperative mortality and morbidity. In addition, substantially more data are needed to determine whether decreasing preoperative opioid use will lead to a decrease in perioperative mortality, morbidity, and other outcomes, including length of hospital stay and incidence of hospital readmission. Finally, investigators should attempt to determine the threshold at which any potential benefits may occur (i.e. what percentage decrease in preoperative opioid use is needed to affect postoperative outcomes).

Intraoperative Considerations

Analgesia in Patients With Obstructive Sleep Apnea

Surgical patients with obstructive sleep apnea (OSA) pose significant challenges in the management of postoperative pain. This issue is complicated by the fact that a large percentage of patients with OSA (e.g. 26% of adults in the United States) are not diagnosed at the time of surgery.[25] Unrecognized severe OSA has been associated with an increased risk of postoperative mortality and morbidity, including an increase in 30-day postoperative cardiovascular complications.[26]

Although the standard tool to diagnose OSA is polysomnography (i.e. sleep study), it may not be completed prior to surgery or even feasible for large numbers of patients. The STOP-Bang questionnaire was specifically developed to meet the need for a reliable and easy-to-use screening tool for OSA.[27] The STOP-Bang consists of eight dichotomous (yes/no) items related to the clinical features of sleep apnea, and patients can be classified for OSA risk based on their scores. Published guidelines recommend minimizing opioids and sedatives postoperatively for the perioperative management of patients with OSA.[26]

Intraoperatively, the use of regional rather than general anesthesia is associated with a reduced incidence of major perioperative complications such as the need for mechanical ventilation, reintubation, and pulmonary/cardiac complications.[28] Postoperatively, the use of regional analgesic techniques with only a local anesthetic-based regimen (when possible) and multimodal analgesia is preferred as a study in which OSA patients who received more than two additional non-opioid analgesia modes showed significantly lower odds of gastrointestinal complications, need for mechanical ventilation, and critical care admission.[29]

Well-designed and well-executed prospective randomized controlled trials (RCTs) would help determine the optimal postoperative and post-discharge analgesic regimen for OSA patients. Although non-opioid analgesics are recommended for patients with OSA, some non-opioid analgesics are associated with sedation, which may not be ideal for OSA patients. A study on the acute effects of gabapentin on sleep breathing in older men noted that gabapentin worsened sleep breathing acutely compared with placebo.[30] Finally, the "safety" of undertaking surgical procedures in an outpatient setting for those patients needs to be explored further. However, more recent data support the notion that moderate-risk, high-risk, or diagnosed OSA can safely undergo outpatient and advanced ambulatory surgery without extended stay or hospital admission and avoiding adverse postoperative outcomes.[31]

Pharmacologic Chronic Pain Management

Pharmacologic treatment of chronic pain starts with the use of acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs). However, other drugs, such as tricyclic anti-depressants or anti-convulsants, are usually added in case of an associated neuropathic or nociplastic component. Opioids have been over-utilized in chronic non-cancer pain patients in the last few decades, which has contributed to the opioid epidemic and a significant increase in opioid addiction in this patient population.[32] However, opioids are still considered the most effective analgesic for patients with cancer pain.[33]

Acetaminophen

Acetaminophen (paracetamol) was considered as the "analgesic of first choice" for many years, even though it is viewed as a weak analgesic.[33] Besides its well-known hepatotoxicity with higher doses, cardiovascular (CV) and gastrointestinal (GI) effects have also been noted.[34] Acetaminophen has not been shown to be superior to NSAIDs in the treatment of post-surgical pain[35] or for the treatment of hip and knee osteoarthritis (OA).[36] It was less effective than celecoxib (a selective COX-2 inhibitor) for the treatment of chronic low back pain (CLBP).[37] In the United Kingdom, recent National Institute for Health and Care Excellence (NICE) guidelines do not recommend the use of acetaminophen for patients with LBP. Several ongoing clinical trials are testing the efficacy of acetaminophen compared to opioids for various forms of acute, chronic, and postoperative pain. There have also been investigations into different formulations combining an opioid pain reliever with acetaminophen (i.e. Percocet). One such study (NCT03088826 on clinicaltrials.gov) hypothesized that Percocet containing morphine immediate release (MSIR) would provide greater analgesic efficacy than Percocet containing oxycodone at 30 min and 1 h after administration for acute painful conditions. Research is needed to determine the optimal role of intravenous versus oral acetaminophen in perioperative analgesia and oral acetaminophen combinations with other analgesics for long-term pain management.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs represent a large and invaluable group of therapeutic agents used in pain management and are the first choice medications for inflammatory pain, as well as postoperative pain, traumatic pain, osteoarthritis, and rheumatic disorders. A cross-sectional study assessing the prevalence of NSAIDs reported a growing prescription trend, particularly in patients older than 60 years, female sex, and those with underlying heart conditions. However, long-term use of NSAIDs is not recommended because of serious adverse effects (AEs).[38]

The concept behind selective COX-1 and COX-2 inhibitors is not absolute, and at high doses, numerous NSAIDs antagonize both COX isoenzymes, although caution is required when using NSAIDs because of potential AEs, including CV side effects.[39–42] A newer form of ketoprofen (L-Lysine salt) showed gastro-protective effects.[43] The use of NSAIDs has been associated with GI inflammation, bleeding, ulceration, and/or perforation (impaired prostaglandin-mediated mucosal protection with COX-1 inhibition) as well as increased thromboembolic risk, myocardial infarction (MI), and stroke (increased thromboxane/prostacyclin ratio because of COX-2 inhibition).[44] The statements about the CV side-effect profile of NSAIDs were further reinforced by the FDA in 2015,[45] and even individuals without underlying heart conditions or related risk factors are susceptible to heart attacks and strokes with the use of NSAIDs.

The important decision of whether to use COX-2 selective (c2s) or nonselective (ns) NSAIDs in pain management must be made after first estimating the patient's odds of developing GI and CV AEs. This was explored by two RCT trials (PRECISION and CONCERN studies) and a meta-analysis.[46] In comparison to naproxen and ibuprofen (ns NSAIDs), celecoxib (c2s) had a comparable CV safety profile and was advantageous with respect to GI and renal AEs (PRECISION study). Similarly, in the high-risk GI population, celecoxib was found to be superior to a combination of naproxen and proton pump inhibitors (CONCERN study). Ongoing clinical trials are investigating the effect of NSAIDs use on opioid consumption. Another phase four clinical trial is currently attempting to optimize NSAID use by determining whether naproxen taken twice daily before the start of menses has a better effect on dysmenorrhea and bladder pain than naproxen taken on the first three days of menses (NCT03697720 on clinicaltrials.gov). Studies are needed to determine the incidence of CV and bleeding AE for the short-term use of NSAIDs during the perioperative period.

Opioids

A recent systematic review and meta-analysis showed a statistically significant, but small, improvement in physical functioning and pain but with a much greater risk of side effects when opioids were compared to placebo and similar benefits of non-opioid alternatives used in different types of chronic pain (neuropathic, nociceptive, central sensitization, or mixed types of pain).[47]

Opioids cause many AEs such as vomiting, constipation, drowsiness, nausea, and dry mouth in addition to misuse. The FDA has been mandating and encouraging the development of new "druggable" molecules to decrease the current opioid crisis. A potential pharmacologic approach could be evaluated in the future using tissue-targeted selective opioids. It was found that μ opioid receptors displayed pH-sensitive binding. Therefore the activity of its agonist NFEPP ([{±}-N-{3-fluoro-1-phenethylpiperidin-4-y1}-N-phenylpropionamide]) is achieved in an acidic environment, which is expressed in inflamed tissue and can be limited to peripheral action only.[48]

Tramadol and Tapentadol

Besides their μ opioid receptor agonist activity, these drugs are also norepinephrine (tramadol and tapentadol) and serotonin (tramadol) reuptake inhibitors. Tapentadol has minimal effects on serotonin. With this dual pain management approach, practitioners can go "half" up the "ladder" and still achieve substantial pain control very early in the pain development process.[49] Tramadol provides relief of moderate to severe pain, such as LBP, OA, soft tissue surgeries, and total hip arthroplasty surgery. Physical function and social wellbeing were sufficiently improved when tramadol was used to control pain in patients with postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN).[50,51] Several studies evaluating tramadol, tramadol/acetaminophen, and tapentadol deemed them superior to placebo[52] or an active compound, such as oxycodone, pregabalin, codeine/acetaminophen, or NSAIDs, in people with CLBP.[53,54] They expressed low to moderate AEs such as dizziness, nausea and vomiting, a low incidence of GI bleeding, and lower AEs such as dizziness, nausea, vomiting, low incidence of GI bleeding, and lower withdrawal rate compared with morphine or fentanyl. Multimodal analgesic combinations provide complementary and synergistic mechanisms of action and are promising avenues for pain relief. For instance, there is ongoing research into the use of fixed-dose combinations of weak opioids such as tramadol with NSAIDs such as diclofenac. This particular combination has shown a safe, effective, and to be well tolerated.[55]

Anti-depressants (Tricyclic Anti-depressant, Selective Serotonin Reuptake Inhibitor, and Serotonin and Norepinephrine Reuptake Inhibitor)

Tricyclic anti-depressants (TCA) have been used for a long time in the treatment of neuropathic pain conditions (PDN, PHN, painful polyneuropathy, post-mastectomy pain, post-stroke central

neuropathic pain).[56] TCAs express analgesic effects in much lower doses than the ones used for depression management.[57,58] Besides inhibiting the reuptake of norepinephrine and serotonin, TCAs can have significant AEs when they interact with histamine, cholinergic receptors, and cause blockade of ion channels.[59] Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is approved by the FDA for the treatment of PDN, fibromyalgia (FM), and chronic musculoskeletal pain.[60] Patients with CLBP and neuropathic components had better outcomes when receiving duloxetine than placebo and with a similar AE rate.[61] Milnacipran (SNRI) was approved by the FDA for FM associated pain.[62] The two selective serotonin reuptake inhibitors, fluoxetine and paroxetine, have been shown to alleviate pain and improve the quality of life better than placebo in patients with FM.[63,64] Both duloxetine and paroxetine improved quality of life and reduced pain intensity in patients with PDN.[65,66] TCAs, such as amitriptyline, are routinely administered as co-analgesics in pain management. However, they only provide relief for approximately one in three patients. Clinical trials of genetic determinants of anti-depressant efficacy for pain treatment (such as NCT02256943 on clinicaltrial.gov) hypothesize that more knowledge on how cytochrome variants influence experimental pain and side effects will help better predict the response of patients.[67]

Anti-convulsants

Carbamazepine acts by decreasing the excitability of A-δ and C neuronal fibers through the stabilization of voltage-gated sodium channels. The FDA approved it for neuropathy treatment in patients with trigeminal neuralgia but not in other neuropathic disorders.[68] Dizziness, somnolence, and altered gait are the most commonly reported AEs with Stevens-Johnson syndrome, blood dyscrasias, and toxic epidermal necrolysis noted as serious AEs.[69] A decrease in neurotransmitter release by calcium influx modification can be achieved by gabapentin, thus regulating neuropathic pain safely. A crossover study found that gabapentin was associated with mild effects on pain but with significant reversal of sensory loss in patients with complex regional pain syndrome (CRPS).[70]

Both gabapentin and pregabalin are effective for painful PDN, PHN, painful polyneuropathy, spinal cord-, and cancer-related pain. Some AEs were recorded with gabapentin use, such as dizziness, somnolence, and ataxia, which led researchers to the efforts of pregabalin development.[71] Pregabalin has been shown to exhibit a stronger analgesic potential and better effect on sleep and quality of life improvement compared to gabapentin in patients with PHN and PDN, while the nature of its AE profile remains open for further investigation.[72–74] In CLBP patients, pregabalin had similar efficacy as celecoxib. However, the combination of the two drugs was more effective than either monotherapy.[75] In patients with FM taking anti-depressants for concomitant depression, the use of pregabalin significantly improved their pain.[76] Despite the well-defined molecular targets of gabapentinoids, more research is needed into its mechanism of action, particularly in the brain. There is also a need for more studies to correlate patient responses with genetic, epigenetic, and phenotypic characteristics.[67]

Topical Treatments

Topical NSAIDs (diclofenac, ibuprofen, and ketoprofen) have been developed to decrease systemic administration and associated AEs and are widely studied and used. They provide short-term anti-inflammatory effects in addition to pain relief in chronic pain patients.[77] In a study assessing diclofenac sodium patch versus control patch in chronic myofascial pain of upper trapezius muscle, statistically significant pain relief was recorded.[78]

Lidocaine blocks the activity of sodium channels in peripheral neurons when used appropriately and does not result in significant plasma drug levels.[60] In patients with peripheral neuropathic conditions, topical lidocaine 5% patch was proven to decrease pain. However, it was no more effective than placebo in patients with CLBP.[79] For myofascial pain syndrome (MPS) patients, treatments with lidocaine 5% patch alone and in combination with 0.5% bupivacaine over one painful area were both superior over placebo.[80,81]

Topical capsaicin has been found to have stronger analgesic potential than placebo in patients with chronic non-specific LBP.[82] Either topical or spinal delivery of capsaicin or its analog (resiniferatoxin) can desensitize the TRPV-1 receptor, which leads to analgesia. This analog has been used in a cancer-induced dog model to achieve persistent anti-hyperalgesia.[83] As a TRPV-1 receptor activator, capsaicin at a topical high dose increases calcium influx, resulting in the disruption of neuronal fiber nociception. When a capsaicin patch was used in MPS, no significant pain reduction was noted over placebo or NSAID patches.[84] A high dose of capsaicin (8%) was found to be effective in providing pain relief for patients with PHN, sustainable for 12 weeks.[85]

In recent reports, treatment of CLBP with botulinum toxin type A (BoNT) showed superior pain relief compared to placebo.[86] Injections of BoNT exhibit their effects by inhibiting inflammatory mediators and neurotransmitter release, thus decreasing pain in PHN, trigeminal neuralgia, PDN, and intractable neuropathic pain condition.[87] Pain was found to be significantly decreased within a week after a single intradermal injection of BoNT-A in PHN patients, lasting for 12–16 weeks.[88] However a trial evaluating BoNT-A intradermal injection in patients with CRPS with allodynia found it be ineffective and poorly tolerated.[89] In general, BoNTs were proven as a good therapeutic approach for persistent pain states with long-lasting irreversible effects. Studies assessing the effects of BoNT on cervical MPS patients showed a positive outcome in pain reduction. However, when lumbar MPS efficacy over placebo was evaluated, negative findings were noted for BoNT application. The inconsistencies among BoNT studies come from poor study design.[90] In a study where a light chain of BoNT-A neurotoxin was conjugated with substance P, chronic pain patients were successfully treated for nociception upon intrathecal delivery.[91] Bupivacaine, a long-lasting local anesthetic, may be applied topically with the use of a film-forming spray, providing an easy and durable application.[92] More research into the efficacy of this delivery method would be of interest.

Monoclonal Antibodies

Monoclonal antibodies are derived from large B-cell glycoproteins, with long half-life immunoglobulin isotopes chosen to provide an extended pharmacologic response with less frequent applications. A recent review analyzed studies involving the use of monoclonal antibodies in chronic pain[93] and found that specific signaling pathways involved in peripheral neuronal inflammation (nerve growth factor [NGF], calcitonin gene-related peptide [CGRP], epidermal growth factor receptor [EGFR], tumor necrosis factor-alpha [TNFα], and ion channels) can be targeted by monoclonal antibodies in several chronic pain states such as migraine, neuropathic pain, OA, CLBP, and cancer pain. This type of therapy can cause mild AEs, but it is rarely prescribed because of high production costs. The pharmacokinetic properties, safety, and tolerability of many monoclonal antibodies are areas of interest for investigation.

Tanezumab is one of the most commonly used nerve growth factor inhibitors designed to modulate pain, stiffness, and physical function in chronic pain related to OA.[94] In general, anti-NGFs are well tolerated with mild AEs such as arthralgia, myalgia, headache, and burning sensations. In a study of CLBP patients, tanezumab was superior to placebo and naproxen sustained even in a long-term extension study.[95] Anti-CGRP monoclonal antibodies were first used in migraine-related pain conditions. However, they have recently shown potential in reducing somatic, inflammatory, and neuropathic pain as well. More severe AEs were noted in phase II clinical trials with monoclonal antibodies against CGRP, such as abdominal and back pain, fatigue, coronary vasoconstriction, and liver toxicity.[96]

Newer Pharmacologic Options

Cannabinoids

The use of cannabinoid compounds relies on the activation of CB1 (spinal neurons, dorsal root ganglia, brain, primary sensory nerves) and CB2 (spinal ganglia, microglia, monocytes, macrophages, B and T lymphocytes) receptors. CB1 receptor activation can reduce pain peripherally and centrally, while CB2 receptor activation decreases the release of inflammatory cell mediators.[97] CB1 receptor alterations are responsible for nociceptive processing when agents that block endogenous CB1 metabolism increase its concentration and activate receptor function. Spinal and peripheral sites of action have been identified in animal neuropathic pain models.[98] CBD receptor agonists modify the cytokine profile by blocking peripheral immune tissue receptors and could be a potential treatment for chronic pain diseases.[99] In the review by Fitzcharles, RCTs were assessed after exploring the efficacy, tolerability, and safety of cannabinoids in chronic pain from FM, back pain, OA, and rheumatoid arthritis.[101] Insufficient evidence was collected to recommend the use of cannabinoids in chronic pain management as the slight superiority of cannabinoids over placebo or amitriptyline was not sustainable. Nabilone (cannabinoid 1 agonist) was shown to improve pain and quality of life in patients with FM[102] and DPN.[103] Newer combinations of cannabinoid CB1μ opioid receptor agonists expressed strong anti-nociceptive effects in several experimental models.[104]

Many states have or are in the process of approving the use of cannabis for medical purposes. However, we still have a long way to go until cannabis is integrated into medical practice. It is difficult to derive the exact dosage for specific conditions while balancing the effectiveness and abuse potential.[100]

Nectar 181 (NKTR181) or Oxycodegol

This agent is a selective μ-opioid agonist. The results of a clinical trial found that NKTR-181 was a safe and effective alternative for patients with CLBP.[105] Despite its advantages, such as low blood–brain barrier permeability and lower abuse and addiction potential over oxycodone,[106] the FDA denied the approval of this drug in January 2020 because of potential misuse because snorting or injecting the drug would increase its rate of crossing the blood–brain barrier. The company has decided to withdraw the nondisclosure agreement for oxycodegol and to stop further program investments.[107] Nonetheless, selective μ opioid agonists remain a promising avenue for the development of analgesic drugs, and future research may be warranted.

Oliceridine (TRV130)

Oliceridine is a novel dual signaling molecule with opioid efficacy. However, it has better tolerability and greater safety than morphine.[108] TRV130 is called a biased ligand because it acts on GPCR μ receptors via G-α protein with weak effects on the β-arrestin pathway, thus producing analgesia with limited side effects such as respiratory depression.[109] In contrast to morphine, the specific nature of the dual pathway of oliceridine allows for comparable or better therapeutic efficacy and a more favorable risk-benefit ratio for moderate to severe acute pain following abdominoplasty.[110] After a denial from the FDA in November 2018, a new drug application was resubmitted in February 2020, and the fate of this pain treatment is yet unknown. Future research is needed to determine its potential role in pain management.

Kapa (kKOR) Opioid Family of Agonists

These agonists have peripherally restricted action, minimal abuse potential, and a low number of AEs, yet possess a significant pain control component which make them promising candidates for future.[111]

Bisphosphates

Bisphosphates (BPs) have been shown to be effective in the treatment of CRPS with improvements in both pain and quality of life when IV alendronate,[112] clodronate,[113] pamidronate,[114] or neridronate[115] were used over placebo. The mechanism of action of BPs in CRPS patients is not well characterized because their ability to reduce bone reabsorption by osteoclastic inhibition is not believed to be important in these patients. The evidence for the therapeutic efficacy of oral and intravenous BP formulations in CRPS is promising. However, there is an unmet need for large, well-conducted RCTs to validate these results.[116]

Immune Signaling

The anti-inflammatory cascade releases interleukin (IL)-4 and IL-10 cytokines, which play a significant role in several animal neuropathic models. IL-10 was effective in the management of chronic peripheral[117] and PDN models.[118] A double-blind, placebo-controlled trial showed that immune globulin intravenous (IGIV) resulted in significant pain reduction in patients with refractory CRPS.[119] Toll-like receptor (TLR-4) antagonists showed significant results relating to inflammatory mediators and neuropathic pain states, and prospective therapies could include spinal delivery of TLR antagonists (lipopolysaccharide-RS) for acute to chronic pain prevention.[120,121]

Lipid Mediators

Several lipid mediators have been found to have anti-hyperpathogenic and anti-inflammatory effects. For example, prostaglandins derived from omega-6 fatty acids have peripheral anti-inflammatory and central effects on spinal excitability.[122] Mediators derived from omega-3 long-chain fatty acids have been metabolized by soluble epoxide hydrolases in their signaling cascade. Therefore enzyme inhibitors have proven to have statistically significant anti-hyperpathic effects in preclinical studies.[123] One of the mediators of the self-healing properties of inflammatory pathways is endogenous proresolvins. In inflammatory and polyneuropathic

models, these molecules possess significant antihyperpathic.[124] Currently, at the preclinical stage of drug development, a newly discovered pro-resolving lipid mediator termed maresin 1 (MaR1) was found to relieve neuropathic pain via a novel mechanism for inhibiting pyroptosis.[125]

Sodium Channel Blockers

For many years, sodium channel blockers (mostly studied NA_V 1.7, 1.8, and 1.9 channel isoforms) have been used in trigeminal neuralgia treatment, specifically carbamazepine and oxcarbazepine. Oxcarbazepine was shown to be significantly better in pain reduction for patients with PDN than placebo.[126] BIIB074 is a relatively new, selective Na_v 1.7 antagonist, capable of inhibiting the firing of trigeminal neurons, with no serious AEs observed.[127] Studies on VX-150, a Na_v 1.8 inhibitor, in acute pain after bunionectomy (NCT03206749) showed promising results; studies on knee osteoarthritis (NCT026660424) and small fiber neuropathy (NCT03304522) have also been completed. Tetrodotoxin (TTX) is another sodium channel antagonist, isolated as a toxin from puffer fish, and has been shown to have long nerve blockade effects in animal and human studies.[128] The future directions of sodium channel blocking drug development will be on small bioavailable molecules as selective antagonists expressing only nociceptive properties.

N-Methyl-D-aspartate Antagonists

Since nociception in FM patients depends on excitatory glutamate activity on N-Methyl-D-aspartate (NMDA) receptors, the significance of NMDA antagonists in the management of this condition may be very useful. In FM and CRPS, ketamine is widely used as a non-competitive NMDA antagonist, in addition to acting on opioid muscarinic, GABA, and non-NMDA glutamate receptors. Ifenprodil is another NMDA inhibitor recently tested in clinical phase 1/2 studies for posttraumatic stress disorder (PTSD) pain.[129] Memantine and dextromethorphan are also used, but with great caution because of the side effects of dizziness, nausea, and sedation.[130] Ketamine[131] and memantine[132] both showed statistically significant differences in pain scores in FM patients, but only memantine was superior to the placebo group. In PHN treatment, topical ketamine was not effective for pain score reduction.[133] Evidence shows that ketamine may be an effective analgesic among select patient populations. Future studies would help determine the efficiency of ketamine among other populations, such as pediatric patients, and investigate alternative routes of administration.[134]

Calcium plays a significant role in cell homeostasis, and the largest groups of receptors within calcium channels are TRPV1 and TRPA1. Inflammatory, neuropathic, visceral, and cancer pain, as well as migraines, are highly dependent on TRP channel activity. This channel alone is associated with diabetes and cancer neuropathies, as well as chronic pain. Thus genetic or pharmacologic blockers have great potential to control these types of pain.[129]

Neurokinin

This type of therapeutic approach was developed to target the neurokinin (NK) receptor as part of the dorsal horn of the spinal cord and is involved in anti-nociceptive tolerance and opioid-induced hyperalgesia. Studies have shown that NK1 receptor inhibition leads to the control of hyperalgesia and conduction in chronic neuropathic pain cases.[135] Ongoing research is investigating the structure affinity/activity of hybrid peptides acting as opioid agonists and NK receptor antagonists. Future experiments, including conformational analyses and molecular docking studies, would promote drug development at this target.[136]

Gene Therapy

Gene expression can be modified by using viral vectors. A multicenter, dose-dependent, phase I clinical trial in patients with cancer showed that intradermal injection of intermediate and high doses of NP2 resulted in significant pain relief.[137] Adeno-associated virus vector transfection of genes that regulate voltage-gated potassium (Kv) channels can contribute to the relief of neuropathic pain.[138] Gene therapy by herpes simplex viral vector delivery of effectors to interleukin 4, 6, 10, or tumor necrosis factor-alpha (TNFα) can be used to decrease morphine intolerance and withdrawal symptoms. In animal models, intrathecal or viral, vector delivered interleukin 4/10 demonstrated efficacy in chronic neuropathic pain models.[139] TNFα inhibitor (infliximab) was discontinued in a double-blind, randomized, placebo-controlled CRPS study as it failed to improve impairment level scores and the overall outcome.[140] Overall, these types of treatments could be beneficial over multiple daily medication dosing regimens while being highly specific for the target. Such treatments would attenuate significant AEs of traditional pain relief methods. However, study designs must be carefully designed. One of the spinal function modifications could be achieved by intrathecal delivery of transfection systems where transcription factors are altered and protein synthesis is affected. The same could be achieved through intraganglionic injections, from which pathologic protein expression in pain patterns can be altered.[141,142]

Non-pharmacologic Chronic Pain Management

Interventional Pain Management

The past two decades have witnessed a dramatic rise in the number of interventional pain procedures performed,[143,144] which has led to increased scrutiny from payers, regulatory bodies, and the lay press. The reasons for the increased scrutiny include an absence of evidence for more procedures to reduce the prevalence of chronic pain or the rate of surgery, and the conflicting evidence, based on predominantly small, low-quality studies, to support their use.[145,146] In one review, the perspective of the provider(s) performing a randomized trial or an evidence-based review had a marked effect on the findings, with interventional pain providers being more likely to experience positive outcomes in clinical trials and reach positive conclusions in review articles, which suggests both the importance of patient selection and technique as well as the possibility of bias.[147]

Obstacles

There are numerous obstacles involved in performing placebo-controlled trials for pain interventions, including the ethical considerations of performing invasive sham procedures, recruitment, high costs to conduct interventional trials, lower return on investment for funding sources (unlike drugs, a company that sponsored a positive trial on intervention would not be the sole financial beneficiary), and unique issues surrounding patient selection and

technique.[148] For example, many patients with LBP have multiple pain generators that can be difficult to identify and isolate, with significant overlap between presentations. Regarding the procedures themselves, technical aspects can also affect the probability of success (e.g. transforaminal versus interlaminar epidural steroid injections [ESI], particulate versus non-particulate steroids, size and orientation of electrode for radiofrequency ablation, intra- versus extra-articular injections for sacroiliac joint blocks).[149,150]

Given the obstacles enumerated, there has been a paucity of placebo-controlled studies evaluating pain interventions, with most containing small numbers, short follow up periods, and serious methodologic shortcomings. For facet radiofrequency ablation and sacroiliac joint injection studies, the controlled trials with the largest numbers of patients enrolled 81 and 24 participants, respectively, with the sacroiliac joint study following patients for only one month.[151,152] This has led to questions about efficacy from payers and referral sources and, in some cases, has resulted in methodologically suspect comparative-effectiveness studies being misinterpreted as demonstrating a lack of efficacy.[153] For ESI, there is widespread agreement that the procedures are more effective than no treatment, but disagreement on the duration of benefit, the magnitude of effect, and even what constitutes a true placebo, as a systematic review found that epidural non-steroid injections afford greater benefit than non-epidural control injections.[154,155] Conventional spinal cord stimulation (SCS) is impossible to evaluate in placebo-controlled trials because of the inability to mask sensations, although high-frequency and burst stimulation are amenable to sham comparisons. However, to date, studies comparing verum to sham stimulation have all been characterized by small numbers (≤40 patients) and short follow up periods (<4 weeks).[156]

Comparative and Cost Effectiveness

Comparative and cost effectiveness studies are of increasing importance in the evaluation of high-cost, high-risk interventional pain procedures, particularly in those that need to be repeated, such as ESI and radiofrequency ablation. Cost effectiveness analyses have been performed for various chronic pain interventions,[157,158] but many are characterized by a lack of equipoise and unrealistic or speculative assumptions. Cost-utility analyses address the question of whether or not a procedure should be undertaken, which presupposes efficacy. Both cost effectiveness and cost-utility analyses are heavily contingent on factors such as whether interventions enable pain patients to work, reduce the need for surgery, and reduce the need for high-risk interventions such as chronic opioid therapy, which in turn reflects patient selection and myriad other factors.[159,160]

Comparative-effectiveness research involves the direct comparison of existing healthcare interventions to determine which works best for which patients and which poses the greatest benefits and harms. There are few high quality comparative-effectiveness studies for interventional pain treatments; one large, multicenter, randomized study found that ESI plus conservative therapy was superior to either ESI or conservative therapy as stand-alone treatments.[161] Many studies, particularly those on SCS, have included a treatment arm in which individuals receive conventional medical management that most have already failed.[162] An implicit form of bias in these studies is that they were recruited by physicians who provide the service(s) being compared to non-interventional therapies and are usually offered the opportunity to crossover to the intervention arm if they fail to derive benefits. In addition, multiple studies have shown that procedural interventions are associated with a higher placebo response rate than medications.[163,164] Given the growing number, utilization, and costs of procedural interventions and the accompanying scrutiny that has ensued, large-scale, prospective comparative and cost effectiveness studies are urgently needed.

Predictive Modeling

Identifying individuals likely to respond to pain treatments has been identified as a top priority by the National Institute of Health (NIH) Federal Pain Research Strategy Task Force.[165] Phenotyping, as it pertains to pain medicine, involves predicting treatment responses based on observable characteristics. Although factors such as technique can affect outcomes, patient selection is by far the most critical factor. In accordance with the biopsychosocial model of pain, factors that could affect interventional treatment outcomes might include the type and degree of pathology (e.g. individuals with a herniated disc respond better to ESI than those with spondylosis without nerve root compression), concomitant psychopathology (e.g. depression), concomitant medical conditions (e.g. sleep disorders, inflammatory arthritis), and social factors (e.g. job satisfaction and secondary gain).

Phenotyping has been advocated by the IMMPACT group in clinical trials,[166] but has not been widely used in clinical practice. One avenue by which this may be facilitated is the development of predictive models based on large-scale registries. For example, it is generally appreciated that individuals with axial low back pain, who are on opioids, with ongoing secondary gain, and who have failed multiple treatments may be less likely to respond to ESI and SCS, but quantifying the probability of success is nearly impossible. Genotyping is more commonly used to predict the response to analgesic medications (e.g. pharmacogenetics for opioids) and may also play a role in procedural interventions, especially those involving drug delivery (e.g. intrathecal delivery systems, ESI, and joint blocks). Identifying likely responders can profoundly impact the results of efficacy studies and cost effectiveness analyses.

Biomarkers

Pain is inherently subjective, and studies have generally demonstrated a poor correlation between imaging findings and pain perception.[167] The lack of any objective means to identify and quantify pain and to measure the response to treatment has led to widespread calls to explore the use of biomarkers, which may include diverse tools such as imaging (e.g. functional MRI and positron emission tomography), molecular (e.g. genomic, proteomic, metabolomic), psychophysical (e.g. conditioned pain modulation, quantitative sensory testing), and behavioral (e.g. facial expressions, fear-avoidance) indices. Biomarkers can be divided into various categories, including risk assessment, diagnostic, prognostic, predictive, and evaluative biomarkers. Discovering new biomarkers and evaluating existing candidates was identified as a key research priority by the NIH Federal Pain Research Strategy.[165]

Regenerative Medicine

Most of the leading causes of chronic pain, including spinal pain and arthralgia, result from degenerative processes that are a consequence of repetitive stress or acute traumatic events. Regenerative medicine involves the process of replacing, engineering, or regenerating human tissue to restore or establish normal functions. It can involve the use of autologous or homologous stem cells, platelet-rich plasma, and placental derivatives, among others. At the molecular level, regenerative medicine may involve stimulating the body's intrinsic repair

mechanisms and/or supplementing these pathways by using autologous or homologous biologic agents when the body is incapable of healing itself. The conceptual advantage of regenerative medicine is that it employs natural substances, thereby reducing the likelihood of adverse reactions, including infection, when autologous tissue is involved. However, regenerative medicine is not devoid of risks, depending on the cell source and location, including localized inflammation, immunologic rejection, and abnormal tissue growth, including tumor formation.[168] Widespread complaints of unsubstantiated claims of effectiveness, inappropriate use, and unanticipated complications led the FDA in November 2017 to issue a comprehensive policy framework to guide the development and oversight of regenerative medicine products. Areas ripe for investigation in this area include identifying patients and conditions most likely to benefit, optimizing treatment protocols (e.g. tissue types and cell numbers), and evaluating long-term effectiveness.

Non-interventional Chronic Pain Management

As we learn more about chronic pain being a perceptual phenomenon, we need to refocus our thinking away from pathologic tissues and onto aberrant perceptions originating in the brain.[169,170] How does one "fix" a perception, and what tools are needed? The answers to these questions represent gaps in our knowledge as well as opportunities for future research. There are likely to be at least three complex processes that can manifest as the perception of pain.[171,172] Each process appears to respond differentially to different classes of treatments,[173] yet currently, we lack efficient methods of detecting which processes and mechanisms are active within a given patient. One type of pain that we are learning a great deal about through large NIH-funded research networks such as the Orofacial Pain Prospective Evaluation and Risk Assessment study (OPPERA; NIDCR/NIH)[174] and the Multidisciplinary Approach to the Study of Pelvic Pain (MAPP; NIDDK/NIH)[175,176] is the concept of central sensitization. This mechanism is thought to be responsible for up to half of all chronic pain cases, which are labeled collectively as the "chronic overlapping pain conditions" (COPCs). Currently, there is a lack of standardized means of assessing COPCs in a given individual. The lack of such a classification tool has hampered the ability to study the overlap of these conditions in a large number of cases. Psychologically based therapies are likely to play increasingly important roles in pain management, as these types of interventions directly impact cognitive and affective neurocortical processes involved in pain perception.[177] However, a challenge to clinicians is how to make these psychological therapies available to patients at low cost and with little burden. Pain self-management, which uses many aspects of these psychological therapies, can be delivered to patients digitally, which is more convenient for patients and clinical practice. While going digital seems to be an attractive clinical option, it is still a young and emerging field with many pros and cons needing consideration before application. Symptom tracking is a component of self-management, and its role in self-management has recently expanded to facilitate shared decision making within the patient-provider dyad.

The use of symptom tracking in combination with digital technology facilitating N-of-1 study designs allows the patient and provider to directly compare the impact of two potential interventions on symptoms for a given patient. This technology brings us closer to personalized pain management.

The following sections provide more details about gaps and future considerations for identifying pain types, identifying COPCs, and using digital self-management approaches and about the future potential of using N-of-1 trials for personalized pain self-management.

The Value of Identifying Types of Pain and Underlying Processes

The International Association for the Study of Pain (IASP) has defined three types of pain.[171,172] The first is called nociceptive pain, which arises from the activation of nociceptors associated with actual or potential tissue damage. It can be inflammatory in nature and usually represents the mechanics of a functioning protective system for the organism. This form of pain is typically not associated with somatosensory nervous system dysfunction. The second type of pain is referred to as is neuropathic pain, which results from lesions to the somatosensory nervous system (either peripheral or central).[178] This form of pain is clearly associated with a dysfunction in the processing of pain. The final mechanism is type of pain is called nociplastic pain. This form of pain arises from functional changes in how the central nervous system processes nociceptive information.[171,178,179] Minimal nociceptive information is augmented by the central nervous system processes resulting in pain. This type of pain may also be thought to be a disordered process.

In any given individual, one or more pain types may be active to varying degrees. For example, it is possible for an individual with OA, a primary nociceptive pain condition, to have comorbid features of a nociplastic condition (e.g. FM) as well. In studies of OA hip and knee replacement, patients with features of nociplastic pain had a 20%–25% greater risk of failure and had greater opioid requirements for pain relief than those without nociplastic features.[180,181] Similar findings have been reported for medial branch blocks[182] and hysterectomy.[183] We also know that medications that tend to work well for nociceptive forms of pain (e.g. NSAIDs) may work less well in the context of nociplastic pain; the latter responds better to centrally acting compounds (e.g. gabapentinoids, NSRIs).[184]

Future clinical practice would ideally be able to match medications with underlying pain type(s). To conduct studies that match medications to pain types, we need better assessment tools to identify the active mechanisms within a given patient (i.e. biomarkers as discussed previously). High quality assessment of pain mechanisms can in part be accomplished using quantitative sensory testing (QST) and neuroimaging modalities.[185–198] While such approaches have revealed useful research about the composition of the various types of pain, these methods remain primarily impractical in the clinical setting. Ideally, QST could be engineered for delivery in the clinical environment, and valid patient-reported outcome measures for indexing neuroimaging findings could be validated for use in clinical settings. Efforts aligned with these suggestions are currently in progress in several studies in the United States and United Kingdom and represent an exciting future direction that could support broader and more efficient attempts to target treatments to the underlying mechanisms of pain.

The Value of Identifying the Chronic Overlapping Pain Conditions

Currently, it is estimated that 100 million individuals experience pain in the United States.[199] In Europe, the estimate is 150 million across 37 countries.[200] Of these, it is estimated that nearly half

may have one or more of the 10 conditions currently identified as COPCs.[201,202] COPCs are generally more prevalent in females than in males and consume billions of healthcare dollars annually.[201,202] The conditions comprising COPCs include, but should not be limited to, temporomandibular disorders (TMD), FM, irritable bowel syndrome (IBS), vulvodynia (VVD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), interstitial cystitis/painful bladder syndrome (IC/PBS), endometriosis (ENDO), chronic tension-type headache (cTTH), migraine headache (MI), and non-specific CLBP.

Historically, most of these conditions have been studied as single conditions without considering their overlap with other conditions. Future research will explore common mechanisms across these conditions and study the degree of overlap among the conditions. Early studies exploring the degree of overlap in such conditions generally support the idea that with greater numbers of overlapping conditions, however the clinical course becomes more challenging.[203]

One barrier to studying COPCs is the lack of a simple method for assessing all 10 conditions within the same individual. It would not be clinically feasible to administer the diagnostic criteria for all 10 conditions to the same person. A potential solution to this problem has been to use ICD10 codes to develop computable phenotypes for each of the 10 conditions, followed by a search for overlapping diagnoses within administrative databases.[220] One study using this approach found that the top three COPCs were CLBP, MI, and IBS. The least common were VVD, ENDO, and urologic chronic pelvic pain syndrome (UCPPS). Some COPCs appeared to have a greater likelihood of comorbidity than others. FM, for example, showed a strong likelihood (odds ratio >5) of co-occurring with seven of the other conditions (e.g. IBS, UCPPS, CLBP, and MI). In contrast, cTTH had substantially lower odds ratios of co-occurring with any of the other COPCs. Still, they had greater odds of co-occurring with any COPC than with other medical conditions.[220] Future studies will want to explore why some conditions co-aggregate more than others and whether there may be temporal influences on when each condition emerges over time.

The Value of Understanding Central Sensitization

It has been suggested that the dominant underlying pain type for many chronic pain conditions (including COPCs) may be nociplastic and therefore would differ mechanistically as well as in treatment response from nociceptive or even neuropathic forms of chronic pain.[173,205–207] A key component of nociplastic pain is the concept of central sensitization. First described by Woolf[208,209] and later translated into clinical assessment criteria,[169] central sensitivity manifests with the following features: (1) pain not because of neuropathic pain; (2) pain not because of nociceptive or inflammatory processes; (3) pain following a widespread distribution (i.e. not localized); (4) the presence of sensory hypersensitivity (e.g. sensitivity to light, sounds, tastes, touch, odors), and (5) the presence of symptoms associated with increased "mental load" (e.g. problems with mood, sleep, cognition, and fatigue).

Sensory hypersensitivity is often assessed using QST and has been found to play a role in many of the COPCs (e.g. TMD,[210] MI,[211] ENDO, pelvic pain,[212,213] cLBP,[214] and FM[215]). "Mental load" can be associated with the concept of increased symptom burden or a diminished state of "wellness." A symptom cluster involving problems with sleep, pain, affect, cognition, and energy (SPACE; see Chapter 61 on self-management) has been identified as an indicator of unwellness in both animal and human models.[216–219] The assessment of each symptom within the SPACE symptom cluster can provide clinicians with a way to prioritize pharmacologic and non-pharmacologic treatment options. Targeting any one symptom within the cluster is likely to confer benefits to pain and overall "mental load" (e.g. treating sleep can help pain).[204] Future research will focus on assessing sensory hypersensitivity and symptom clusters conferring increased mental load. Such phenotypes are likely to inform both the course of treatment and serve as meaningful outcome endpoints for treatment improvement.

Digital Pain Management Resources

Digital pain management resources take many forms, including telephone-based coaching,[221] interactive voice response self-management (IVR),[222] digital devices combined with artificial intelligence,[223] digital versions of cognitive and behavioral self-management,[224–226] digital versions of acceptance and commitment therapy (ACT),[227,228] self-management on websites or for smartphones,[229,230] and virtual reality programs for pain control.[231] Digital pain management resources have the advantage of being available to patients 24/7, tend to be less costly than in-person office visits, and are more convenient as they do not require driving long distances to obtain care.[232] Given the current demands on time for office visits, digital pain management resources also help to broaden care beyond what can be offered in a relatively brief office visit.

Online pain management resources are plentiful and widely accessible, ranging from free to relatively costly subscription services. Recent work in this area has focused on key components of what should be included in such programs to make them effective.[232] Such components include techniques that enhance self-efficacy (e.g. relaxation, exercise, sleep hygiene), social support, monitoring (e.g. symptoms and behaviors), and a means of structuring the intervention such as goal setting, action planning, and shared decision making with a healthcare provider. The latter category, a means of structuring the interventions, is often missing from most digital programs, with the majority of online or smartphone programs offering a more limited set of resources (e.g. relaxation techniques or pain symptom monitoring). More challenging and more rarely encountered are programs that automate goal setting, problem solving, action planning, or shared decision making. In the 900 plus smartphone apps claiming to offer pain management, the majority included only a few of the easiest modules to digitize.[230] To enhance the effectiveness of digital pain management resources, it is important to include more of the components that have historically made traditional face-to-face interventions effective.

Another challenge facing digital pain management interventions is that most programs have been developed without any pain expertise,[233] and most programs available to the public have not been subjected to clinical trials.[230,233,234] The few programs that have been developed by pain experts and that have been studied clinically usually come from academia with grant funding rather than a sustainable business plan. Thus unfortunately, once the grant ends, support for the digital program expires. Most evidence-based digital self-management programs are not available to the public.[235] A challenge for the pain treatment community going forward will be to construct business models that support the development, testing, and sustainability of such resources.

Expanding the Value of Symptom Tracking: Personalized Medicine Using N-of-1 Trials

Informed clinicians try to apply evidence based medicine in their practice. The evidence often comes from large RCTs or even meta-analytic studies of multiple RCTs.[236] The problem with blanket recommendations from evidence based sources is that RCTs and meta-analytic studies aggregate large amounts of data to describe the outcomes for a statistically averaged individual. Thus an individual with the characteristics of the "average" patient in these large trials may not exist in the real world. As individuals deviate from this average because of clinical history, demographics, or other factors, their heterogeneity can diminish expected outcomes.[237] An alternative to clinical recommendations based on big data is the use of little data, or N-of-1 trials.[238]

Part of self-management is monitoring symptoms and behavioral changes over time (see Chapter 61, Patient Education and Self-Management). Such longitudinal monitoring has the advantage of revealing patterns in symptoms for the individual (e.g. pain tends to worsen on weekends compared to during the week, or fatigue is worse in the mornings compared to later in the day). Identification of such patterns provides data for the individual with which they can generate hypotheses about why the pattern exists and what can be done about it. Historically, there has not been any standardized approach to using symptom monitoring data, and patients were largely on their own to interpret and find benefits from the revealed patterns. Recently, symptom monitoring has been performed at the next level in terms of its potential utility. Patients can be their own scientists and discover what works best for them using a structured N-of-1 experimental design combined with symptom monitoring.

N-of-1 trials are single-patient crossover trials that can leverage the patient-provider relationship by studying whether two or more treatments work well in a given individual. N-of-1 trials can be conducted in "real world" settings and work best in chronic conditions such as pain and for treatments with rapid onset and washout (e.g. NSAIDs, massage, acupressure, meditation, exercise, sleep hygiene methods). Such trials benefit from the use of a smartphone app or wearable technology to capture daily ratings of symptoms and AEs and weekly adherence data. Patients also need to decide which symptom (or set of symptoms) is being targeted by the interventions (e.g. sleep, pain, mood).

The provider and patient work together to develop an N-of-1 trial design in which two treatments are selected and the order of treatment use is randomly determined (e.g. treatment A [two weeks], treatment B [two weeks], treatment A [two weeks], treatment B [two weeks]). After the trial is completed, the patient and provider evaluate which intervention had the best impact on the selected symptom(s) chosen as the outcome. Depending upon the results, the patient has proof of something working or knows which treatment options should be reconsidered.

"Trialist" is a smartphone app that facilitates N-of-1 trials.[239] Analytics of patient end-user experiences with N-of-1 methodology found that patients were generally enthusiastic about recording their information and accessing their own data. Despite highly informative reporting and graphing functionality, patients tended to prefer simpler/minimalist graphs of data. Providers, on the other hand, may find more complex data more informative. Patients also valued the ability of the data to provide insights into their condition of which they had forgotten or were unaware. The partnership between the patient and provider trying different options together and allowing patients to participate in informed decision making was also identified as a benefit of this approach.[240] The broader use of the N-of-1 methodology is a likely future direction for facilitating personalized pain self-management.

Exciting directions for future work include improving our ability to assess for the types of pain so as to improve our ability to match treatment to the hypothesized processes involved. One type of pain, nociplastic pain, is the newest classification and is thought to be driven by central sensitization. Central sensitization is a relatively new phenomenon in need of additional studies given its association with hyper-sensory sensitivity and symptom clusters that overlap with pain processing. Clinically, there has been an expansion of digital options for receiving pain care, but the quality of these offerings is often untested. While digital options typically offer specific skills, they often lack much of the goal setting and treatment planning that is essential to the provider-patient relationship. Future studies will aim to better integrate these elements of care into digital offerings. Personalized pain medicine represents a broad field in need of additional studies, much of which will involve non-interventional approaches.

Conclusions

Despite numerous advances in the investigation of pain medicine over the past decades, there are many gaps in our knowledge of treatments in the areas of perioperative pain management, pharmacologic, interventional, and non-interventional chronic pain management. In the area of perioperative pain management, the development of ERPs, elucidation of mechanisms, and effective treatment for CPSP are needed. In the area of pharmacologic chronic pain medicine, the development and role of newer analgesic agents need to be researched further. Additional studies using placebo-controlled trials for pain interventions and comparative/cost effectiveness studies are needed for interventional pain management, along with more research in predictive modeling, biomarkers, and regenerative medicine. Finally, in the area of non-interventional chronic pain, additional research is needed to identify COPCs and utilize digital pain management resources.

Key Points

- Advances in perioperative pain management will revolve around patient-centered outcomes and recovery (enhanced recovery after surgery).
- Optimization of perioperative opioid management is paramount.
- High quality placebo-controlled trials for interventional pain medicine are needed.
- The ability to identify underlying pain mechanisms will facilitate personalized pain medicine.
- COPCs likely share a common underlying mechanism of central sensitization.
- Studying how and why COPCs overlap will broaden our knowledge of central sensitization.
- Digital self-management resources can extend clinical practice but currently are limited in what components of self-management are offered and with variable quality.
- Shared decision making between patients and providers can be informed by the use of N-of-1 trials comparing two treatment options for an individual patient.

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